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Studies in the Epidemiology of Syphilis

III. Conjugal Syphilis. A Statistical Study of a Series of 226 Married Patients Whose Spouses Were Examined

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INTRODUCTION

A PREVIOUS communication (1) contains certain details regarding the results of examinations of sexual contacts and of nonsexual family contacts in 996 cases of acquired syphilis which were studied at the syphilis clinic of the Vanderbilt University Hospital. The present paper deals with the question of conjugal syphilis among 226 of these patients whose marital partners were examined.

Clinicians have the impression that infectiousness of persons with syphilis diminishes to the point of extinction by the fifth year of the disease. Since the advent of compulsory premarital examinations, it has become even more important than formerly to determine the validity of this opinion, which is based largely on studies of conjugal syphilis and relatively meager statistical data on infections relapse.

Almost 60 years ago, Fournier (2) discussed the factors which should be considered before granting an infected person permission to marry. He mentions

active treatment and clinical quiescence, but especially emphasizes the time factor. Fully 30 years ago, Sir Jonathan Hutchinson (3) wrote: "Most authorities are agreed that, as a rule, patients who have reached the sixth year of their disease, although they may themselves be still liable to symptoms, do not transmit."

Payenneville (4) recommended prophylactic treatment for the husband or wife exposed to a syphilitic spouse. A course of six preventive injections of neoarsphenamine apparently protected against infection in 10 individuals exposed to primary and secondary syphilis; the treatment failed in 1 case. Jordan (5) reported that in 23 percent of 117 families, syphilis was limited to 1 marital partner. The duration of the disease in the infected individual was not considered. Of the 100 cases in which both partners were affected, Jordan found 94 instances in which wives were infected by their husbands, and 6 instances in which husbands were infected by their wives. In 72 of the wives of infected husbands symptomatic syphilis developed and in 22, latent syphilis. In the 6 men infected by wives primary syphilis developed.

Levitin (6) stated that if the syphilitic infection is old in one marital partner, the spouse may never become infected. He mentions Metschersky's report of 47 families in which all of the mothers and 18 of the children had syphilis. The husbands of these women were free of the disease. Levitin also reports the case of a

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woman who was infected by her first husband at the age of 20. She was divorced 2½ years later and remarried at the age of 25. The second husband was seronegative 3 years after this marriage, but a chancre developed 2 months after his wife started treatment. The possibility of extramarital infection was not excluded.

Dennie (7) in 1927, considered the age of the infection to be the most important factor in its transmission. Hall (8) stated that 90 percent of infected husbands acquire syphilitic infection before marriage, and 67 percent of infected wives acquire infection from husbands who were infected before marriage.

Thompson (9) briefly reviews the studies of conjugal syphilis by Stokes, Fournier, Blaisdell, Keyes, Solomon, and Strandberg. Fournier, he states, found that 75 percent of married women with syphilis acquired the disease from their husbands. In Stokes' experience more than 90 percent of sexual exposure to syphilis in men is antemarital. Keyes estimated the chances of establishing conjugal infection by the untreated husband as 12 to 1 the first year of the disease, 5 to 2 the second year, 1 to 4 the third year, and practically negligible the fourth and fifth years. Among 208 couples studied, Strandberg found that 27.6 percent of the marital partners escaped infection; he indicated that in 20 percent the disease was transmitted to the partner later than the fifth year of infection. In two cases transmission took place after the eighth year of infection.

Twenty-three percent of the spouses of 64 married patients with primary or secondary syphilis observed at the syphilis clinic of the Vanderbilt University Hospital (1) escaped infection.

Greenbaum, Katz and Rule (10) asked the question: "When can a male patient under treatment for syphilis safely marry?" In untreated patients, they state, "transmissibility to others is a question of (1) duration of the infection in the contaminated individual—the older the infection the less the chances of transmission; (2) the presence of open lesions (and here again the earlier the infection

the greater the infectiousness of the lesions); (3) the infectiousness of secretions—saliva, vaginal secretions, blood, and semen, in particular; (4) tissue reservoirs with relapsing lesions and spirochetic sorties into the humors. The second factor is rapidly eliminated by treatment, and it has often been assumed that the same is true for the third factor." The authors recall the experiment of Eberson and Engman who inoculated rabbits with the semen from 17 patients with chronic syphilis. Six of the rabbits died. In two of the remaining 11 signs of syphilis developed. One of these had been inoculated with semen from a patient with early latent syphilis who had never received antisyphilitic treatment; the second, with semen from an individual who acquired syphilis 13 years previous to the experiment and had received oral medication only during the first 3 years of his disease. Greenbaum, Katz and Rule inoculated rabbits with single semen specimens from 25 patients, 6 of whom had been infected less than 4 years, 2 for an unknown period, and 17 for more than 4 years. All had been treated for varying periods. None of the rabbits developed evidence of syphilitic infection. The authors concluded that their experiment demonstrated the noninfectiousness of semen from patients under treatment.

Kemp (11) was unable to demonstrate by rabbit inoculation the infectiousness of semen from 15 men with syphilis of more than 4 years' duration, 6 of whom were untreated. He reviewed the literature on the subject and collected 119 instances of inoculation with semen from patients the duration of whose infection could be determined. Sixty-seven men had early syphilis (syphilis of 4 years' duration or less) and 52 had late syphilis. In 19.4 percent of the 67 early cases, infectiousness of semen was demonstrated, and in only 1.9 percent (one case—Eberson and Engman, 1921) of the late cases was it possible to demonstrate infectiousness.

Decker (12) in 1934 summarized contributions to the literature on the subject of conjugal syphilis, and reported

376 families in which at least one marital partner had syphilis and in which both partners were examined. Sixty infected husbands and 98 infected wives had non-syphilitic spouses. In 218 families both husband and wife were infected. Decker concluded that infectivity varies inversely with the duration of the disease. Among 59 cases of conjugal syphilis reported by Galliot (13), the husband was the source of the infection in 56 instances and the wife in 2 instances. In one case the responsibility for the infection could not be fixed.

A concise statement of current views on conjugal syphilis was published recently by O'Leary and Williams (14). They examined the records of 1,175 married couples. In 46 percent both the husband and the wife had syphilis. In this series there were three families in which repeated sexual contacts had occurred while one or the other marital partners had active lesions of the mucous membranes, fluid from which contained *Treponema pallidum*. Prophylactic measures had not been used; nevertheless not one of the marital partners was infected. In 83 percent of the families in which one of the partners had acquired syphilis less than 1 year before marriage both spouses were infected. Nevertheless if less than 2 years had elapsed since the disease had been acquired both members were infected in 33 percent of the families; if less than 5 years had elapsed the partners in 25 percent of the families were both infected; if less than 10 years had elapsed both partners in 15 percent of families were infected. If more than 5 years had elapsed between infection and marriage both members were infected in only 9 percent of the families. However when the estimate of the duration of infection was based on definite, accurate knowledge it was found that very few partners had become infected when the interval between infection and marriage was more than 5 years. Nevertheless these observations seem to indicate that the 5-year interval is by no means an absolute safeguard to the marital partner. There were 18 patients, who

had received 20 or more injections of an arsphenamine and a heavy metal within the first year of the infection and before marriage, who subsequently married within the first 2 years after infection. Six of the partners (33 percent) of these 18 patients were infected. Premarital intercourse on the part of the partners was not excluded.

In the syphilis clinic of the Vanderbilt University Hospital we have had an opportunity to investigate the problem of conjugal syphilis in 226 couples. The material will be presented in tabular form.

TABLE 1.—*The number of infected and noninfected marital partners of 226 original patients examined at the syphilis clinic of Vanderbilt University Hospital*

Original patients		Marital partners			
Race and sex	Number	Infected		Noninfected	
		Number	Percent	Number	Percent
White male.....	55	25	45.5	30	54.5
White female.....	57	35	61.4	22	38.6
Total white....	112	60	54.5	52	45.5
Negro male.....	53	29	54.7	24	45.3
Negro female.....	61	40	65.7	21	34.3
Total negro....	114	69	60.0	45	40.0
Grand total....	226	129	57.1	97	42.9

RESULTS

In table 1 is shown the number of original² patients by race and sex and the number of infected and noninfected marital partners of these patients. Of the total number of spouses, 42.9 percent escaped infection. Syphilis was found in 45.5 percent of the wives of the white men, in 61.4 percent of the husbands of the white women, in 54.7 percent of the wives of the Negro men, and in 65.7 percent of the husbands of the Negro women.

There were 60 instances among white couples and 69 instances among Negro couples where both marital partners were

² The patient who presented himself or herself first for examination.

TABLE 2.—The type of syphilis in 226 original patients and their marital partners

Stage of disease of wives	Stage of disease of husbands										Total
	Negative	Primary	Secondary	Early latent	Late latent	Latent—duration unknown	Benign tertiary	Asymptomatic neurosyphilis	Symptomatic neurosyphilis	Cardiovascular syphilis	
Negative.....	0	4	8	4	18	1	2	4	11	2	54
Primary.....	1	2	0	1	0	1	0	0	0	0	5
Secondary.....	5	3	22	8	1	4	1	0	0	0	44
Early latent.....	5	1	6	11	3	4	0	0	0	0	30
Late latent.....	20	0	1	1	10	14	0	1	1	0	48
Latent—duration unknown.....	3	0	0	2	12	3	6	2	3	0	31
Benign tertiary.....	1	0	0	0	0	2	0	0	0	0	3
Asymptomatic neurosyphilis.....	3	0	0	0	0	1	0	0	0	0	4
Symptomatic neurosyphilis.....	4	0	0	0	0	2	0	0	0	0	6
Cardiovascular.....	1	0	0	0	0	0	0	0	0	0	1
Total.....	43	10	37	27	44	32	9	7	15	2	226

infected. In every instance an attempt was made to determine which partner infected the other. Among the whites the husband infected the wife in 50.8 percent of instances, and the wife infected the husband in 13.1 percent; while in 36.6 percent of the instances it could not be determined which was the source. The corresponding percentages among the Negroes were 33.3, 4.4, and 62.3. Among the white patients 53 percent of the men and 7 percent of the women admitted extramarital sexual intercourse. Among the Negroes 45 percent and 28 percent, respectively, admitted marital infidelity. In considering the instances in which both partners were infected it should be remembered that infection in either or

both partners may have been acquired from extramarital sources.

Table 2 indicates the type of syphilis present in marital partners. From this it can be seen that there were 10 instances of primary syphilis among husbands. Four of the wives of these men had escaped infection at the time the husband's treatment was instituted; two had primary, three secondary, and one early latent syphilis (under 2 years' duration). There were five wives who had primary syphilis. The husband was negative in one instance. Two husbands had primary syphilis, one early latent, and one latent syphilis of unknown duration. There were 37 husbands and 44 wives who had secondary syphilis; in 22

TABLE 3.—The stage of disease in 226 original patients and their marital partners

One spouse diagnosed as—	Number	Other spouse diagnosed as—									
		Negative	Primary	Secondary	Early latent	Late latent	Latent—duration unknown	Benign tertiary	Asymptomatic neurosyphilis	Symptomatic neurosyphilis	Cardiovascular
Negative.....	97	0	5	13	9	38	4	3	7	15	3
Primary.....	15	5	4	3	2	0	1	0	0	0	0
Secondary.....	81	13	3	44	14	2	4	1	0	0	0
Early latent.....	57	9	2	14	22	4	6	0	0	0	0
Late latent.....	92	38	0	2	4	20	26	0	1	1	0
Latent—duration unknown.....	63	4	1	4	6	26	6	8	3	5	0
Benign tertiary.....	12	3	0	1	0	0	8	0	0	0	0
Asymptomatic neurosyphilis.....	11	7	0	0	0	1	3	0	0	0	0
Symptomatic neurosyphilis.....	21	15	0	0	0	1	5	0	0	0	0
Cardiovascular.....	3	3	0	0	0	0	8	0	0	0	0

TABLE 4.—*Presence of syphilis (treated or untreated) before marriage in 226 original patients*

	White						Negro						Grand total	
	Male		Female		Total		Male		Female		Total			
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Disease present before marriage—treated.....	9	16.3	6	10.5	15	13.4	15	28.3	7	11.5	22	19.3	37	16.4
Disease present before marriage—untreated.....	4	7.3	2	3.5	6	5.4	14	26.4	5	8.2	19	16.7	25	11.0
Total.....	13	23.6	8	14.0	21	18.8	29	54.7	12	19.7	41	36.0	62	27.4
Disease not present before marriage or information lacking.....	42	76.4	49	86.0	91	81.2	24	45.3	49	80.3	73	64.0	164	72.6
Grand total.....	55	100.0	57	100.0	112	100.0	53	100.0	61	100.0	114	100.0	226	100.0

instances both spouses had the disease in this stage. Eight wives were uninfected and 5 husbands escaped infection while living with a marital partner with infectious secondary lesions. Unfortunately, it was not determined whether unprotected sexual intercourse took place during the stage of active infection, but it is known that the patients were living together at the time.

Table 3 is derived from table 2 to show more clearly the stage of the disease found to exist in marital partners. Thus, there were 15 instances of primary syphilis among the 452 persons included in this study. The spouses of these patients were negative in 5 instances, had primary syphilis in 4, secondary syphilis in 3, early latent syphilis in 2, and latent syphilis of unknown duration in 1. There were 81 instances of secondary syphilis; the

spouses were negative in 13 of these families.

In table 4 is shown the status with regard to infection before marriage of the original 226 patients and also whether or not treatment for syphilis had been received. Sixty-two patients gave a history of premarital infection—13 (23.6 percent) of the white men, 8 (14 percent) of the white women, 29 (54.7 percent) of the Negro men, and 12 (19.7 percent) of the Negro women. This represents 27.4 percent of the original patients—18.8 percent of the whites and 36 percent of the Negroes. Others may have been infected at the time of marriage, but we were not able to secure a history of infection.

In addition there were 13 spouses of original patients whose infection could be dated prior to marriage, making a total of 75 (16.6 percent of the 452 original patients and spouses) who were known to

TABLE 5.—*The effect of duration of infection and of premarital treatment on conjugal syphilis*

Spouses of original patients	Original patients—duration of disease before marriage							
	Less than 4 years				4 years or more			
	Untreated		Treated		Untreated		Treated	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Spouse infected.....	1	12.5	5	41.6	0	0.0	0	0.0
Spouse escaped.....	7	87.5	7	58.4	13	100.0	12	100.0
Total.....	8	100.0	12	100.0	13	100.0	12	100.0

have contracted syphilis before marriage. Of the 25 whites and 50 Negroes in this group, 6 (24 percent) of the former and 23 (46 percent) of the latter had received no treatment whatever for syphilis before marriage.

Table 5 gives some indication of the relation between the duration of the disease and the amount of treatment received, and the infectiousness of syphilis. No conclusions can be drawn from these figures but the results correspond with the general impression and with the experiences of others. All of the spouses included in this table denied extramarital exposure; it was our impression that we could rely on their statements.

There was no instance of conjugal infection of spouses of patients whose disease had been present 4 years or more before marriage, whether treated or untreated.

Infection of marital partners did take place when the infection was of shorter duration (less than 4 years). It is interesting that a higher percentage of infected spouses was found among those whose partners had received some treatment, inadequate in all instances, before marriage than among those who received none.

SUMMARY

1. A summary of some of the literature on conjugal syphilis is presented. The general impression prevails that the incidence of conjugal transmission is low if the infection in the syphilitic spouse has been present for 4 or more years before marriage.

2. An analysis is given of 452 records representing 226 married couples studied by us. Both marital partners were infected in 57.1 percent of the cases. The husband alone was infected in 23.9 percent and the wife alone in 19 percent of the cases. Thus in 42.9 percent of this group of marital partners one member escaped infection.

3. A larger number of men than women admitted extramarital sexual relations. The number of cases in which the husband infected the wife is definitely

greater than that in which the wife infected the husband. It is emphasized that in a large number of cases the marital partner responsible for the infection could not be determined.

4. Eighteen out of 96 marital partners escaped infection in spite of the fact that their spouses had infectious lesions of the skin or mucous membranes.

5. Syphilis had been acquired before marriage by 18.8 percent of the white and by 36 percent of the Negro marital partners of the original patients. No treatment was received prior to marriage by 24 percent of the white and 46 percent of the Negro patients who had contracted syphilis before marriage.

6. Marital infection was not observed in any individual whose spouse had acquired syphilis more than 4 years before marriage.

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Studies in the Epidemiology of Syphilis

IV. The Value of Patient Education in Controlling the Spread of Syphilis

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INTRODUCTION

SUCCESS in the control of syphilis depends upon the discovery and the extermination of the reservoirs of infection. Discovery of these reservoirs depends upon an increased sense of awareness on the part of the medical profession of the ubiquity of syphilis, upon the "Wassermann drag-net", and upon proper attention to contact investigation. They are exterminated by early and adequate treatment.

That syphilis is an epidemic disease has long been recognized. The part the physician plays in disclosing and controlling epidemics of syphilis has been frequently emphasized, and its wide distribution has often been pointed out (1, 2, 3, 4, 5, 6, 7). The value of the "Wassermann dragnet" is universally acclaimed. The investigation of syphilis contacts has proved its worth through the discovery of numerous instances of infection (8).

There are ample means for the discovery of individuals who are responsible for the perpetuation of the infection. Unless each individual is rendered non-infectious by adequate treatment, however, time spent in case-finding is largely wasted. Infectious relapse decreases in frequency with increasing numbers of arsphenamine injections. Studies of the

Cooperative Clinical Group (9) have shown that 64 percent of patients with early syphilis who received one to four injections of an arsphenamine relapsed, while only 14 percent of those who received five to nine injections relapsed. When 20 or more injections were received, less than 2 percent of patients experienced infectious relapse. A previous study by the same group (10) indicated that 35 percent of all infectious relapses occur in patients who have received less than 5 doses of arsphenamine, 65 percent in those receiving under 10 doses, and 87 percent in those receiving under 20 doses.

The attainment of treatment ideals in a given case of syphilis is directly proportional to the patient's understanding of his illness. The informed patient cooperates in carrying out treatment schedules; the confused or perplexed patient draws his own conclusions as to the time for cessation of treatment, and usually the disappearance of signs and symptoms is his criterion of cure. The value of instructing the syphilitic patient has been demonstrated in studies by others (4, 11, 12, 13, 14.) The present report supplies additional data relative to this point. All of the patients included in our study were members of the clientele of the syphilis clinic of the Vanderbilt University Hospital.

MATERIAL STUDIED

The patients were divided into two groups. The first group, classified as "casually instructed", includes new patients with syphilis who entered the

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syphilis clinic during the period from September 1, 1935 through August 31, 1936. The second group, "carefully instructed" by one of us (E. G. C.), entered the clinic during the period September 1, 1937 through August 31, 1938. The system of social service follow-up of delinquency was essentially the same during the two periods. There were 443 patients admitted during the first period and 560 during the latter.

Fifteen percent of the first group and 11 percent of the second group were ex-

cluded from the study because of death or because of transfer to another clinic or physician. Patients with late symptomatic syphilis are also excluded from both the groups. Thus, the clinical material in the study is comprised of cases of early symptomatic syphilis (primary and secondary) and asymptomatic syphilis (latent, early, and late).

The patients in the two groups were classified according to race and sex. The material is arranged in table 1 according to these facts.

TABLE 1.—*Race, sex, and diagnosis of patients in the casually instructed group and in the carefully instructed group*

	Casually instructed 1935-36		Carefully instructed 1937-38	
	Number	Percent	Number	Percent
Early symptomatic (primary and secondary only):				
White male.....	45	34.6	40	32.8
White female.....	31	23.8	22	18.0
Negro male.....	32	24.6	29	23.8
Negro female.....	22	17.0	31	25.4
Total.....	130	100.0	122	100.0
Total white.....	76	58.5	62	50.8
Total Negro.....	54	41.5	60	49.2
Total.....	130	100.0	122	100.0
Asymptomatic (latent):				
White male.....	15	5.1	33	16.1
White female.....	31	10.5	40	19.5
Negro male.....	49	16.6	58	28.3
Negro female.....	199	67.8	74	36.1
Total.....	294	100.0	205	100.0
Total white.....	46	15.6	73	35.6
Total Negro.....	248	84.4	132	64.4
Total.....	294	100.0	205	100.0

There were 130 patients with primary or secondary syphilis in the 1935-36 group and 122 in the 1937-38 group. There were 294 patients with asymptomatic syphilis in the 1935-36 group and 205 in the 1937-38 group. The asymptomatic groups were predominantly Negro.

TYPE OF INSTRUCTION GIVEN

As previously indicated each patient of the carefully-instructed group was instructed by one person. Instruction was invariably preceded by questioning in order to determine the extent of the patient's understanding of the illness.

The content of the instruction was modified according to the patient's insight and emotional reactions (12), the stage of the disease, the marital and economic status, and the treatment requirements. In each instance an attempt was made to present a comprehensive statement relative to the infectiousness of syphilis, its natural course and sequelae, and the effectiveness of adequate treatment. We are impressed of the soundness of Nelson's statement that "unless a patient has been given all of these facts about syphilis, it can hardly be said that he is negligent of self and society in missing

treatments. It is more likely a sign of negligence in the physician when a patient who has not had syphilis explained to him fails to return for his injections (15)."

RESULTS

In table 2 are indicated the number of visits to the syphilis clinic by patients with primary or secondary syphilis during the two periods studied. The treatment for primary and secondary syphilis in this clinic is so standardized that by the time patients have made 37 visits to the clinic they have received a minimum of 20 injections each of an arsenical and a heavy metal. Thirty visits represent a minimum of 20 injections of an arsenical and 13 of a heavy metal; 14 visits, 10 injections of an arsenical and 7 of a heavy metal. The "first course" represents 8 injections of an arsenical and 3 of a heavy metal. The numbers and percentages shown in the table are cumulative.

It can be seen that, when white patients with early infectious syphilis were casually instructed, as was the

case in 1935-36 in this clinic, only 5.2 percent were still under observation at the end of a year and only 32.7 percent received minimum treatment requirements. Fifty percent received 20 arsenical injections and 74.7 percent received as many as 10 arsenical injections. The figures are considerably higher in the carefully-instructed group (1937-38). Here at the end of a year, 19.3 percent were still being treated, 64.4 percent had received minimum treatment requirements, 75.7 percent had received as many as 20 arsenical injections, and 90.2 percent as many as 10 arsenical injections.

Only 16.6 percent of Negro patients admitted during the "casual-instruction" period received as many as 20 arsenical and 20 heavy metal injections, 29.6 percent 20 arsenical injections, and 53.6 percent 10 arsenical injections. Negroes who were carefully instructed maintained a much better attendance record. Only 3.3 percent, however, were being treated at the end of a year. Nevertheless 41.5 percent had received 20 injections each of an arsenical and bismuth, 56.4 percent 20 arsenical injections, and 76.4

TABLE 2.—Number of clinic visits made by casually instructed and by carefully instructed patients with symptomatic early syphilis

Clinic visits	Casually instructed 1935-36		Carefully instructed 1937-38	
	Number	Percent	Number	Percent
Patients with primary or secondary syphilis:				
White:	<i>Cumulative</i>	<i>Cumulative</i>	<i>Cumulative</i>	<i>Cumulative</i>
52 or more visits.....	4	5.2	12	19.3
37 or more visits (minimum; 20 As., 20 Bi.).....	25	32.7	40	64.4
30 or more visits (minimum; 20 As., 13 Bi.).....	38	50.0	47	75.7
14 or more visits (minimum; 10 As., 7 Bi.).....	57	74.7	56	90.2
8 or more visits (minimum; 8 As., 3 Bi.).....	61	79.9	60	96.6
Total white patients.....	76	100.0	62	100.0
Negro:				
52 or more visits.....	0	0.0	2	3.3
37 or more visits (minimum; 20 As., 20 Bi.).....	9	16.6	25	41.5
30 or more visits (minimum; 20 As., 13 Bi.).....	16	29.6	34	56.4
14 or more visits (minimum; 10 As., 7 Bi.).....	29	53.6	46	76.4
8 or more visits (minimum; 8 As., 3 Bi.).....	35	64.7	54	89.6
Total Negro patients.....	54	100.0	60	100.0
Total White and Negro:				
52 or more visits.....	4	3.1	14	11.5
37 or more visits (minimum; 20 As., 20 Bi.).....	34	26.1	65	53.2
30 or more visits (minimum; 20 As., 13 Bi.).....	54	41.5	81	66.3
14 or more visits (minimum; 10 As., 7 Bi.).....	86	66.1	102	83.5
8 or more visits (minimum; 8 As., 3 Bi.).....	96	74.6	114	93.7
Total patients.....	130	100.0	122	100.0

TABLE 3.—*Number of clinic visits made by casually instructed and by carefully instructed patients with asymptomatic syphilis*

	Casually instructed 1935-36		Carefully instructed 1937-38	
	Number	Percent	Number	Percent
Patients with latent (asymptomatic) syphilis:				
White:	<i>Cumulative</i>	<i>Cumulative</i>	<i>Cumulative</i>	<i>Cumulative</i>
52 or more visits.....	1	2.2	8	10.9
37 or more visits.....	11	23.9	48	65.8
30 or more visits.....	14	30.4	58	79.5
14 or more visits.....	24	52.1	69	94.5
8 or more visits.....	32	69.5	70	95.9
Total white patients.....	46	100.0	73	100.0
Negro:				
52 or more visits.....	4	2.7	5	3.8
37 or more visits.....	25	17.0	54	40.9
30 or more visits.....	37	25.2	67	50.7
14 or more visits.....	70	47.6	99	74.9
8 or more visits.....	94	63.9	119	90.1
Total Negro patients.....	147	100.0	132	100.0
Total white and Negro:				
52 or more visits.....	5	2.6	13	6.3
37 or more visits.....	36	18.6	102	49.8
30 or more visits.....	51	26.4	125	61.0
14 or more visits.....	94	48.7	168	81.9
8 or more visits.....	126	65.3	189	92.2
Total.....	193	100.0	205	100.0

percent 10 arsenical injections. Almost 90 percent of these patients completed the first course of 8 arsenical injections.

Table 3 shows the number of clinic visits by patients in the two groups who had asymptomatic syphilis. This table is presented to demonstrate what effect the presence or absence of lesions may have on attendance. This table is to be compared with table 2. During the casual-instruction period clinic attendance was considerably better for white patients with lesions than for those with asymptomatic syphilis. Thus, 74.7 percent of patients with primary or secondary lesions made as many as 14 visits, whereas only 52.2 percent of patients without lesions attained this attendance record. Among the Negroes the difference is not as pronounced. However, the attendance at 14 and 30 weeks was better among those who had symptoms than among those who had none.

During the careful-instruction period the attendance of patients with symptomatic and asymptomatic syphilis was practically identical. This indicates that instruction, and not the presence

of lesions, was the significant factor in stimulating attendance.

The average number of visits per patient with primary or secondary syphilis during 1935-36 was 26 for white and 20 for Negro patients; during 1937-38 it was 38 for white and 29 for Negro patients. The average number of visits per patient with asymptomatic syphilis during 1935-36 was 20 for white and 10 for Negro; during 1937-38 it was 38 for white and 29 for Negro.

It is obvious that clinic attendance in the carefully-instructed group is far from ideal and, in view of the results expected, is very disappointing. At the present time we are planning a more extended and intensive system of instruction based on a study of the patient's mental age in an attempt to improve attendance. A sample of 300 patients taken at random from the syphilis clinic was submitted to the revised Army Beta mental tests² designed for illiterates. A preliminary study of the results in-

² Issued by the Psychological Corporation, New York, N. Y.

icates that there is correlation between attendance record and mental age. Instructed white patients cooperated better than instructed Negroes. The mental age of about 50 percent of our white patients is about the 8-year level. The mental age of 90 percent of the Negro patients is below this level.

It is not practical to submit all patients on admission to the clinic to the Army Beta mental test, therefore we have attempted to find some means of rapid simple examination which will indicate roughly each patient's mental age. One hundred of the above patients were submitted to portions of the test included on the "Abbreviated Filing Record Card for the Stanford Revision of the Binet-Simon Tests".³ A preliminary study of the results indicates that the "Ball and Field" test on these cards may be used to separate patients into two classes, those of low mentality who doubtless will require repeated instruction and those of higher mentality who will probably require less attention. This study is now in progress.

SUMMARY AND CONCLUSION

1. A study of the clinic attendance of two groups of patients, one casually instructed and the other carefully instructed regarding syphilis, is presented in order to demonstrate that patient education plays a major part in insuring adequate treatment for the prevention of infectious relapse.

2. Seventy-six percent of white patients and 56.4 percent of Negro patients who were carefully instructed received 10 injections of arsenicals, whereas only 10 percent and 29.6 percent respectively of the casually instructed received this amount of treatment.

³ Published by the Riverside Press, Cambridge, Mass.

3. Plans are underway to modify and extend instruction for selected patients of low mentality in order to improve attendance further.

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Purification of the Antigen Used in Diagnostic Tests for Syphilis by Means of the Cadmium Salt

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THE EFFECTIVE antigenic substance used in the various standard diagnostic tests for syphilis is present in the lecithin fraction of extracts ordinarily prepared from beef heart tissue. It is, therefore, either a lecithin or a concomitant of lecithin. A number of studies of the antigenic properties of highly purified lecithin have been reported in the literature. The reports of the work of these investigators are conflicting. Weil and Besser (1) with a synthetic lecithin and Fischer (2) with a cadmium-chloride purified lecithin were able to report the presence of antigen activity in these materials. On the other hand, Wadsworth, Maltaner and Maltaner (3) and Fujimura (4) found no activity in cadmium-chloride purified lecithin. Since there is this conflicting evidence regarding the activity of lecithin purified through the cadmium salt, we have carried out the investigation reported in this paper to determine if the fraction is antigenic when used in the slide test for syphilis.

EXPERIMENTAL WORK

The lecithin fractions used in the preparation of the cadmium salts were

This study was made possible by the establishment of a fellowship in the Department of Chemistry of Western Reserve University by Mr. Frank LaMotte of Baltimore, Md., together with funds provided by Mr. A. S. Wimmer and associates of Cleveland, Ohio, the Research Committee of the American Medical Association, and the Division of Venereal Diseases of the U. S. Public Health Service. Assistance in this project was given by the serology division of the Research Committee of the American Society of Clinical Pathologists.

prepared from beef heart in the following way:

Difco beef heart powder was extracted exhaustively with ether in a Soxhlet-type extraction outfit for 24 hours over an oil bath at 50° C. Extraction was then continued with ethyl alcohol by the same method at 100° C., until extraction was practically complete (in 24 hours 85 percent complete). The two extracts were kept separate. The lecithin fractions were isolated from each extract as shown in figure 1 (the weights indicated are the amounts obtained from 2 lb.=900 gm. of powder).

Fractions (A) and (B) were purified further by means of the cadmium chloride salt as described below. The method is essentially that described by Levene and Rolf (5) and by Maltaner (6).

To a 5-percent solution of the lecithin fraction in absolute ethyl alcohol a saturated solution of cadmium chloride in 95 percent methyl alcohol was added until precipitation was complete. The mixture was then centrifuged, and the clear solution was discarded. The waxy precipitate of cadmium salt was taken up in ether (15 parts by weight), and to the suspension 50 parts of ethyl alcohol were added to reprecipitate the salt. The precipitate was collected by centrifuging. This process was repeated twice more. The lecithin was liberated from the cadmium salt as follows: The salt was taken up in chloroform (10 parts) and treated with a 20-percent solution of ammonia in

absolute methyl alcohol. The reagent was added in slight excess of the amount needed for complete precipitation of cadmium hydroxide. The cadmium hydroxide was removed by centrifuging, the supernatant liquid con-

centrated *in vacuo*, and the resulting wax was taken up in ethyl alcohol and again concentrated. In this way the excess ammonia was removed. An average return of 40 percent of lipoid was obtained.

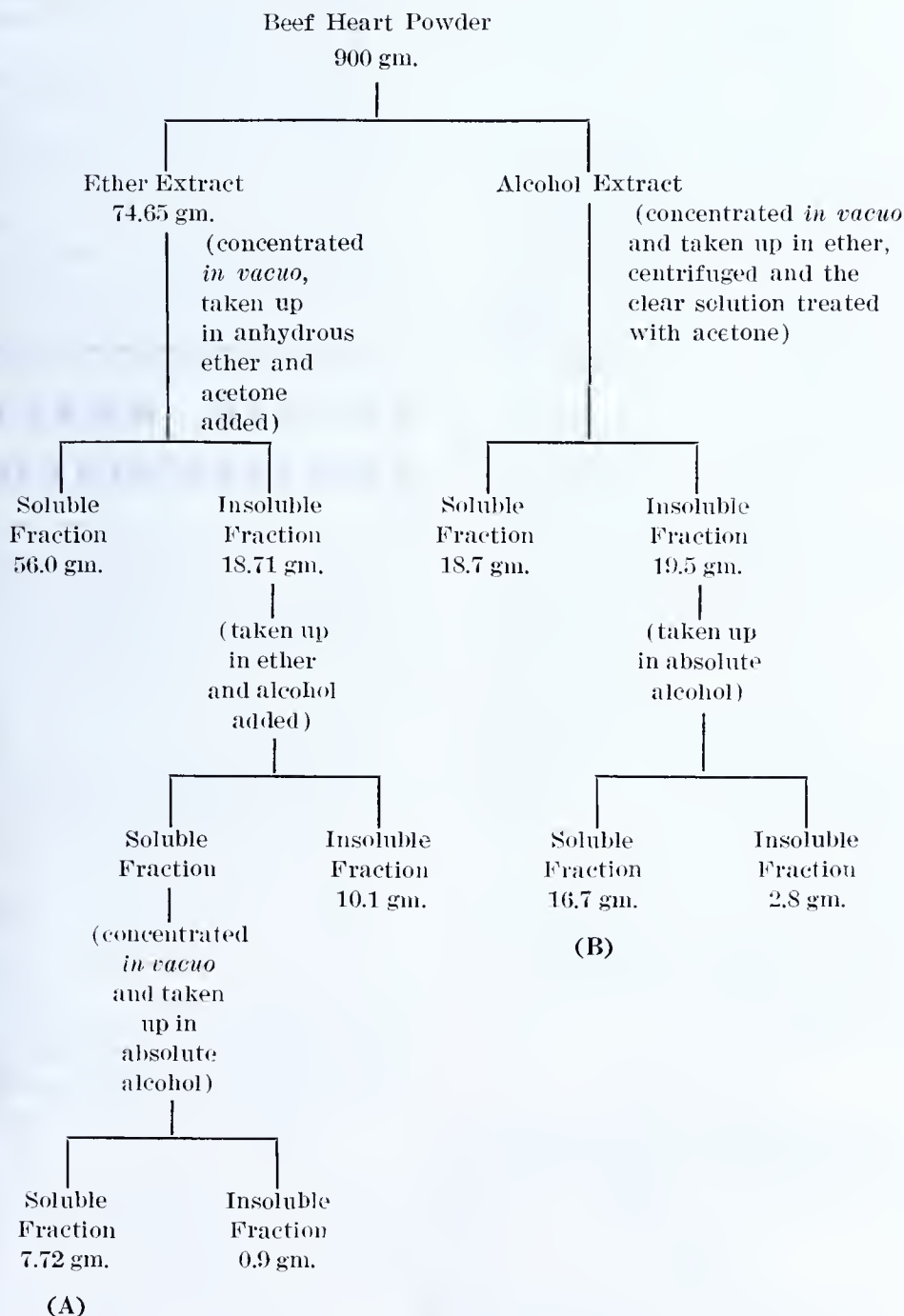


FIGURE 1.

The change in composition resulting from his treatment is shown in the following typical analytical data:

	<i>Starting fraction (A) Percent</i>	<i>Product Percent</i>
Nitrogen (Kjeldahl) -----	1.45	2.07
Phosphorus -----	2.36	3.52
Iodine No. (Hanus) -----	56.6	61.00

These values may be compared with the theoretical values for distearyl lecithin, namely nitrogen 1.77 percent, phosphorus 3.92 percent, and iodine number 0.

The materials prepared from both (A) and (B) were very nearly the same in both antigen potency and composition with respect to nitrogen, phosphorus, and unsaturation.

Antigen titers were made on all samples. The method we have found best consists in diluting a pooled serum through a series of dilutions and determining the dilution which gives a minimal positive reaction in the slide test using as antigens the unknown and a control. The ratio of these critical points, then, was the same as the ratio of the concentration of the antigen preparations. Following this procedure it was found that by treatment with cadmium chloride the antigen titer of our samples had been increased by about 20 percent.

It can be concluded from these results that a lecithin fraction purified through the formation of the cadmium salt not only retains its antigenic activity but also has undergone a measurable increase in concentration of the true antigenic substance.

ACKNOWLEDGMENT

The writers wish to express their gratitude for the help and advice of Dr. B. S. Kline throughout the course of this work.

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PUBLIC HEALTH ADMINISTRATION

National Social Hygiene Day will have its fifth annual observance on February 5, 1941. This year's theme deals with social hygiene in relation to national defense. A concerted drive is to be made to safeguard men in military and naval training camps and in essential industries from the ravages of venereal disease and will include increased effort to reduce commercialized prostitution to a minimum.

Plans for the annual event include more than 5,000 community meetings in all parts of the country and 4 regional conferences to be held in Philadelphia, St. Louis, New Orleans, and Los Angeles.

The American Social Hygiene Association has issued a folder, "We Face a New Challenge", which describes the plan. Quantity lots of this folder for use as an envelope enclosure may be obtained from the American Social Hygiene Association, 1790 Broadway, New York City. The Association also offers to provide a comprehensive group of program and publicity aids and materials for State and community groups, including literature for distribution at meetings.

Prenatal blood tests for syphilis. John Hall. Public Health News, Trenton, 24: 147, Oct. 1940.

The New Jersey law requiring that blood tests for syphilis be made on all pregnant women has been in effect for a year and a half. The birth certificates filed in the State Bureau of Vital Statistics have been carefully examined for six different months to determine the completeness of the information as to whether or not blood tests had been made on the mothers during pregnancy.

For the State as a whole there has been a steady increase in the percentage of certificates which carry the information. In March 1939, 56 percent of the certificates for live births and 32 percent for stillbirths stated that a blood test for syphilis had been made; in May 1940 the percentages were 93 for the live births and 42 for the stillbirths. Failure to use the new birth certificate forms, with the spaces provided for reporting the facts about the prenatal tests, is largely responsible for poor reporting. Considering various factors, Hall feels that at least two-thirds of the women whose babies were born in 1939 had prenatal blood tests.

The time in pregnancy when the tests are made is of special importance. For the mothers whose babies were born alive in March 1939, 22 percent had their test before the fifth month of pregnancy and 20 percent at or near the time of delivery; in May 1940, the percentages for the corresponding periods were 38 and 13.

The Veterans' Administration Facility for Negro beneficiaries, Tuskegee, Ala. Eugene H. Dibble, Jr. M. Bull. Vet. Admin., Washington, 17: 158-162, Oct. 1940.

A relatively large group of the patients at the Tuskegee Facility are suffering from syphilis of the central nervous system. For a number of years it was impossible to treat these patients by malaria therapy as Negro patients did not respond to the tertian strain of malaria which was then in use. However, in 1932, after re-

search and study it was found that the quartan strain of malaria, a foreign strain to which the Negro had not developed an immunity, gave satisfactory results. Since then more than 500 patients have been inoculated, with a large proportion of complete recoveries and returns to gainful employment. The same strain of malaria is still in use at this facility, and blood has been furnished to other Veterans' Administration Facilities and numerous State hospitals from here.

The National Research Council and medical preparedness. J. A. M. A., Chicago, 115: 1640-1643, Nov. 9, 1940.

In order that the latest knowledge may be available to the medical officer, the Army Medical Corps requested that the subcommittees prepare manuals on their specialties. The Surgeon General's office will soon issue a general manual which will include the chemotherapeutic treatment of venereal diseases.

The Subcommittee on Venereal Diseases is composed of J. E. Moore, Chairman; Edwin P. Alyea; Charles W. Clarke; Oscar F. Cox, Jr.; J. F. Mahoney; and John H. Stokes. Eight meetings have been held. The committee has prepared memorandums on the prophylaxis and treatment of all the venereal diseases, utilizing the latest chemotherapeutic agents. It has made suggestions as to venereal disease control, for a standard nomenclature for the diagnosis of syphilis, and, along with many of the other subcommittees, has outlined plans for the training of medical officers.

Syphilis, gonorrhea and the national defense. R. A. Vonderlehr. Bull. Genito-infect. Dis., Boston, 16: 1-2, Oct. 1940.

From past experience the control of syphilis and gonorrhea has been shown to be not only a humanitarian measure, but an important need in the development of an efficient manpower as part of the national defense. In the World War, venereal diseases caused an average of 3 noneffective man-days for every man in the United States Army.

The armed population and the civilian population are so closely linked that an

attack on these diseases must include both groups to be effective. The Medical Corps of the Army, the Bureau of Medicine and Surgery of the Navy, and the Public Health Service have been studying plans for the control of venereal diseases in the national defense program. Their proposed plans have been approved by the Secretaries of War and of the Navy and the Administrator of the Federal Security Agency, and also were indorsed by the Conference of State and Territorial Health Officers.

The responsibility of the Army and of the Navy is defined as developing effective measures for the clinical management of the venereal diseases in the armed forces. Responsibility for the treatment of the infected civilian population is placed on the local health departments. Extramarital contacts of infected persons in the armed forces will be reported to State or local health authorities, and contacts of enlisted men with infected civilians will be reported to the Army or Navy medical officers.

The opportunities for contact with infected persons are decreased by the repression, as far as possible, of commercialized and clandestine prostitution. Very little in this line can be accomplished, however, without the active support of public opinion. An active program of education, particularly as to the dangers from syphilitic infection, the methods of prevention, and the steps which should be taken if infection is suspected, is being carried out. The physician in private practice has an opportunity not only to serve humanity but also to serve his country through cooperation with health authorities in the national defense program.

What blood tests show. Illinois Health Messenger, Springfield, 12: 101, Oct. 1, 1940.

From evidence based on the results of blood tests done on three groups of volunteers and on applicants for marriage licenses it appears that if the entire white population of Illinois were examined about 2 percent would be positive for

syphilis. One of the groups examined consisted of 9,053 persons who took advantage of an offer by the State Department of Public Health at the Illinois State Fair in 3 different years. Of these, 87, or slightly less than 1 percent, were positive. Another group were volunteers at the annual reunion of soldiers and sailors at Salem in 1940. Here 1,117 tests were run on men and women ranging in age from 15 to 60, and of the group 34, slightly more than 3 percent, were positive. The third group consisted of 541,245 white persons in Chicago. Of this group 15,015, about 2.8 percent, were positive. Of the 119,004 persons who complied with the premarital health examination law, 1,838, about 1.5 percent, were found to be positive. In the four groups serologic evidence of syphilitic infection was found in 16,974, or about 2.5 percent.

The prevalence of the disease undoubtedly varies from community to community, as also in different age groups. The rate is uniformly higher among colored than among white people in all the surveys.

Procedure for transmitting syphilis patients from clinics to State hospitals.

Malcolm H. Merrill. Weekly Bull., California Dept. Pub. Health, Sacramento, 19: 134, Sept. 14, 1940.

Reference is made to the statement of Dr. A. J. Rosanoff, Director, State Department of Institutions (Weekly Bull., July 13, 1940), that State hospital facilities are available for fever therapy for cases of neurosyphilis. The recommended procedure for using this service is: (1) Secure voluntary commitment forms. (2) Transmit the completed form to the State hospital to which the patient is to be sent, indicating the date on which admission is requested. (3) After a reply has been received from the hospital, proceed with final details for transferring the patient. (4) Arrange with the patient to return to the clinic after being discharged from the State hospital.

The provision of malarial therapy for cases of syphilis by the State hospitals is a unique and valuable service. Local

clinics and health departments are urged to use this service. During the past 2 years 52 cases have been referred from one clinic to the Stockton State Hospital.

Health education concerning venereal diseases. M. A. Bigelow. J. Social Hyg., New York, 26: 312-315, Oct. 1940.

Bigelow summarizes the report of a study in relation to venereal disease control education, made jointly by the U. S. Public Health Service and the American Social Hygiene Association. The report was based on a reconnaissance of educational activities in this line in about 30 States, and has been read and approved by more than 200 leading health educators.

There is complete agreement that the venereal diseases should be an integral part of courses which deal with other communicable diseases. It is generally agreed that a well-organized health course gives the best setting for lessons on venereal diseases, presented as are tuberculosis or other familiar communicable diseases. There is some opposition to isolated lectures on venereal diseases in schools which do not have health courses, but including them in a series of health lessons is highly approved. Visiting special lecturers on venereal diseases may be useful for students who are not under regular teachers. However, students in high schools and regular colleges do not need the details of special medical lectures on venereal diseases. General facts and a desirable attitude toward the problem are more likely to come from regular health teachers.

The idea in sex hygiene before 1910 that the venereal diseases were the reason for and the goal of sex education has changed. Today the most emphasis in sex education is placed on topics which do not involve the venereal diseases, and venereal diseases have been given their scientific place in studies of communicable diseases in health education. Only 3 of the 200 health educators who were consulted opposed this point of view. This new sharp line between venereal disease education and sex education will require revision of books written years ago.

There are now, therefore, two big educational problems connected with the work of the American Social Hygiene Association; first, a strenuous drive for venereal disease education as an integral part of health education in high schools and general colleges; second, a broad program of education that concerns the normal relations of the two sexes.

LABORATORY RESEARCH

Massive "acute" precipitation of free sulfathiazole in the urinary tract.

David Lehr, William Antopol and Jacob Churg. Science, New York, 92: 434-435, Nov. 8, 1940.

The formation of concretions in the urinary tract after chronic administration of sulfanilamide derivatives has been reported repeatedly in the literature. The uroliths were always found to contain a high percentage of the very insoluble acetylated form of the different compounds.

In the course of an investigation on the acute intraperitoneal toxicity, in rats and mice, of sulfapyridine, sulfamethylthiazole, or sulfathiazole, the peculiar observation was made that all animals dying from a single dose of sulfathiazole, or its sodium salt, without exception, showed massive precipitation of the free drug in the urinary tract. Depending upon the dose, and consequently upon the time-interval between injection and death of the animal, the precipitate was found in different parts of the urinary tract. If death occurred only a few hours after the injection, the collecting tubules and the papillary ducts were filled with a whitish material distinctly visible macroscopically and extending into the renal pelves, ureters, and bladder. After a longer time-interval, the precipitate in the kidneys diminished in amount and finally disappeared (usually after 24 hours), while

the bladder became completely filled and even distended with a white crystalline material which in some cases reached back into the lower parts of the ureters. Within 10 to 20 hours this soft precipitate in the bladder was converted into hard aggregates weighing between 5 and 30 mg. and composed almost entirely of free sulfathiazole. This picture was seen in 54 rats and 20 mice injected with various doses of sulfathiazole or its sodium salt.

This phenomenon of acute precipitation was further investigated by sacrificing groups of 3 rats at different time intervals after the intraperitoneal injection of a sublethal dose of sodium sulfathiazole (1.0 gm. per kg.). The data from this study demonstrate the extreme rapidity of absorption and excretion of sulfathiazole and lend support to the view, expressed previously, that the acute precipitation in the urinary tract is due mainly to a high rate of elimination of sulfathiazole from the body. Thus after concentration of the glomerular filtrate by reabsorption of water, precipitation occurs in the collecting tubules.

A similar picture could not be produced with sulfanilamide, sulfapyridine, sulfamethylthiazole, or their sodium salts.

Additive action of bismuth and arsenic compounds in therapy of experimental syphilis. N. M. Clausen, B. J. Longley and A. L. Tatum. *J. Pharmacol. & Exper. Therap.* (Proc. Am. Soc. Pharmacol. & Exper. Therap.), Baltimore, 69: 281, Aug. 1940.

The employment of combinations of bismuth and of arsenical compounds in the treatment of rabbit syphilis has indicated to the writers that the two agents are simply additive. Fractional parts of the minimal curative dose of these different compounds are equal, in that there is neither potentiation nor inhibition of one compound by the other when they are given together.

Fractions of single curative doses of mapharsen and bismuth sodium tartrate did not sterilize the animals even though more than 50 percent of the minimal curative dose of each compound was used.

This is evidently due to lack of simultaneity of action.

These data suggest that bismuth and arsenical compounds attack the spirochete in a simple additive manner.

The toxicity, treponemicidal activity and potential therapeutic utility of substituted phenylarsenoxides. I. Methods of assay. Harry Eagle. *J. Pharmacol. & Exper. Therap.*, Baltimore, 69: 342-354, Aug. 1940.

The demonstration that mapharsen (m-amino-p-hydroxyphenylarsenoxide) is an effective and safe drug for the treatment of syphilis necessitates a reorientation of ideas with respect to the chemotherapy of that disease. There is no reason to believe that mapharsen is the only phenylarsenoxide of therapeutic utility. The present study is an attempt in the direction of a systematic study of substitute phenylarsenoxides which might possibly disclose a correlation between their chemical structure, toxicity, and treponemicidal activity and thus provide a clue not only to the mechanism of their therapeutic action but also to the development of compounds significantly better than those now available.

The present paper describes the methods which have been used in this study to assay (a) the treponemicidal activity in vitro of a series of phenylarsenoxides, (b) their therapeutic activity in syphilitic rabbits, and (c) their toxicity in white mice and rabbits.

The toxicity, treponemicidal activity, and potential therapeutic utility of substituted phenylarsenoxides. II. Monosubstituted phenylarsenoxides (Cl; NO₂; CH₃; C₂H₄OH; C(CH₃): NOH; NH₂, OH, CH₂NH₂ and derivatives). Harry Eagle, George O. Doak, Ralph B. Hogan and Harry Steinman. *J. Pharmacol. & Exper. Therap.*, Baltimore, 70: 211-220, Oct. 1940.

Twenty-seven monosubstituted phenylarsenoxides have been studied from the point of view of toxicity in mice and rabbits, treponemicidal activity in vitro, and therapeutic activity in syphilitic rabbits.

The toxicity for white mice per gram arsenic ranged between 7 and 120, referred to that of the unsubstituted phenylarsenoxide as 100. Similarly expressed, the treponemicidal activity varied between 21 and 147. Most of the compounds were both less active and less toxic than phenylarsenoxide, i. e., substitution in the benzene ring inhibited both these properties. None of the 27 derivatives would seem as potentially valuable as mapharsen in the treatment of syphilis. The study indicated that different substituent groups may affect therapeutic activity and toxicity in varying degrees, but not necessarily in parallel. It follows that compounds may well be discovered in which the ratio of these two properties is more favorable than it is in mapharsen.

The toxicity, treponemicidal activity, and potential therapeutic utility of substituted phenylarsenoxides. III. Monosubstituted compounds: Acids, esters, benzophenone, methylsulfone. Harry Eagle, George O. Doak, Ralph B. Hogan and Harry Steinman. *J. Pharmacol. & Exper. Therap.*, Baltimore, 70: 221-222, Oct., 1940.

None of the 16 arsenoxides discussed in this paper appears to be of potential utility in the treatment of syphilis. In general, monosubstitution with an acidic group markedly inhibited the activity and decreased the potential therapeutic utility of phenylarsenoxide. Blocking the acidic group, either by esterification, or as in the acetophenone, benzophenone and methylsulfone compounds, largely removed the inhibitory effect of the acid on treponemicidal activity, and with two of the compounds resulted in a ratio of treponemicidal activity: toxicity significantly exceeding that of phenylarsenoxide.

Determination of the optimal ratio of cholesterol to tissue-extract antigen in the complement-fixation test for syphilis. John F. Kent. *J. Immunol.*, Baltimore, 39: 307-315, Oct. 1940.

The details of an investigation of the relations between cholesterol and tissue extract in the complement fixation test

for syphilis, with a view to replacing the empiric basis of adjustment, are reported.

There is an optimal ratio, cholesterol: tissue extract, that exhibits maximal antigenic activity in the complement fixation test for syphilis. With the antigens studied, increase in the ratio, cholesterol:extract, did not result in anticomplementary properties.

To determine the optimal ratio, extract must be tested in such concentrations that the optimal amount of cholesterol will fall within the range of quantities soluble in alcoholic tissue extract. Varying the concentration of alcoholic extract in alcohol does not alter the optimal ratio. Different concentrations of extract require proportionately different quantities of cholesterol for their maximal sensitization.

Varying concentrations of the alcoholic extract in alcohol exhibit the same antigenic activity, provided the optimal quantities of cholesterol are added. Differences in concentration are compensated for in tests by changes in the saline dilutions yielding maximal reactions of given quantities of serum. As a result of these findings, the adjustment of cholesterol and tissue extract for use as antigen in the complement fixation test for syphilis may be based upon that optimal ratio of the two which exhibits maximal antigenic activity. The experimental procedures given offer a practical method for determining this ratio.

A comparative study of toxicity and therapeutic action of bismuth compounds. B. J. Longley, N. M. Clausen and A. L. Tatum. *J. Pharmacol. & Exper. Therap.* (Proc. Am. Soc. Pharmacol. & Exper. Therap.), Baltimore, 69: 294, Aug. 1940.

Toxicity studies in rabbits and therapeutic studies in rabbit syphilis have indicated the similarities rather than the differences in a number of bismuth compounds and therefore suggest that these compounds act in a common manner probably due to a common end product.

The maximal tolerated intramuscular dose of bismuth (metal) in terms of mg.

per kg. was found to be 59 for bismuth sodium tartrate, 40 for bismuth ethyl camphorate, 20 for iodobismitol, 10 for bismuth citrate, and 2 for thio-bismol. In contrast to this wide variation, the intravenous tolerated doses were found to be 3 for bismuth ethyl camphorate, 2 for bismuth sodium tartrate, bismuth citrate and iodobismitol, and 1 for thio-bismol.

The triple curative dose of bismuth (metal) was 2 mg. per kg. for bismuth ethyl camphorate, 1.5 mg. per kg. for thio-bismol, and 1.0 mg. per kg. for bismuth sodium tartrate, bismuth citrate and iodobismitol. The single curative doses of bismuth ethyl camphorate and bismuth sodium tartrate were 7 mg. per kg. and 3 mg. per kg. respectively.

These data seem to indicate that bismuth compounds ultimately act in a form common to all and not in the form of the compound in which they were injected, and the observed differences of the many compounds may be accounted for largely by the differences in the rate of absorption from the intramuscular deposits.

PATHOLOGY

Allergic phenomena in ophthalmology.

Alfred Appelbaum. Arch. Ophth., Chicago, 24: 803-823, Oct. 1940.

Experimental analogy indicates that certain cases of syphilitic interstitial keratitis may be definitely allergic. In 1911 Wessely suggested that syphilitic interstitial keratitis might be related to anaphylaxis. Animal experimentation led him to the conclusion that the condition was due to the specific corneal hypersensitivity and intoxication. Igersheimer pointed out that in hereditary syphilis the cornea contains spirochetes which sensitize it to the condition. If spirochetes come to life subsequently in another part of the body and liberate their toxins in the blood, an anaphylactic reaction in the hypertensive cornea results. This is interstitial keratitis.

Others have been unable to demonstrate spirochetes in the cornea in this condition.

Clinically there are certain observations which suggest that the keratitis in some cases may be allergic. The sudden occurrence of interstitial keratitis in a patient under active treatment for syphilis with preparations of the heavy metals while the infection is elsewhere following a favorable course has often been noted (also, the stubbornness of the condition to treatment with arsenicals). If actual invasion of the cornea by spirochetes takes place in all instances of this condition, a definite improvement in the eye would be expected to follow arsenical treatment, since it is known that arsphenamine injected intravenously rapidly reaches the cornea. Hence, an inference is drawn that in certain cases recurrent interstitial keratitis in persons with congenital syphilis is probably an allergic phenomenon, a sensitization of the cornea being produced through invasion by spirochetes either in fetal life or early in the course of the disease. Subsequently, the syphilitic status being altered somewhat by the arsenical treatment, large amounts of disintegrating syphilitic virus are liberated. This when carried to the eye in the blood or lymph, produces an intoxication of the sensitized cornea, clinically manifested as interstitial keratitis.

Arsphenamine encephalopathy. Report of unusual clinical and histologic observations. Norman A. Levy. Arch. Dermat. & Syph., Chicago, 42: 814-821, Nov. 1940.

A 19-year-old white youth was admitted in coma to the Michael Rees Hospital October 28, 1939. About 6 months previously manifestations of secondary syphilis had developed, especially condylomata lata. He was treated with 2 injections of a bismuth preparation and 4 intravenous injections of neoarsphenamine, the last injection being 3 days before admission to the hospital. The day following the injection he complained of headache, vomited, and had

temperature of 102° F. In the afternoon of the day of admission he suddenly went into coma.

The clinical diagnoses considered were acute syphilitic meningitis with encephalitic involvement or acute hemorrhagic encephalopathy with meningeal hemorrhage due to arsphenamine intoxication. In view of the meningitic syndrome with a polymorphonuclear pleocytosis and a positive Wassermann reaction of the cerebrospinal fluid, a diagnosis of acute syphilitic meningo-encephalitis was made and treatment with large doses of intravenous iodides was begun. The patient failed to rally, his temperature went to 108° F., and he died during the night. A necropsy was performed.

On gross examination of the brain the numerous small hemorrhages observed pointed to hemorrhagic encephalopathy due to arsphenamine, possibly complicating syphilitic meningitis. However, the histologic findings were unlike syphilis of the brain. The vascular lesions, the hemorrhagic and inflammatory changes in the parenchyma, and the meningitic reaction were ascribed to the toxic effect of the arsphenamine.

Syphilitic (gummatous) pulmonary arteritis with rupture into the bronchial tree. A. J. Segal. Arch. Path., Chicago, 30: 911-915, Oct. 1940.

Thirteen cases of gummatous type and 18 cases of the productive cicatricial type of proved syphilis of the pulmonary artery have been reported in the literature. In only one case have spirochetes been demonstrated within the vessel walls.

A 50-year-old white fireman was admitted to the Jewish General Hospital of Montreal complaining of pain in the chest, dyspnea, productive cough, and foul breath of 1 months' duration. He had had several attacks of hemoptysis during the 5 days preceding admission. From 1914 to 1934 he had occasional antisyphilitic therapy. Examination led to a diagnosis of pneumonia and chronic bronchiectasis and also tertiary syphilis. He was discharged as im-

proved after 10 days. Six days later, he was readmitted because of repeated hemoptysis. He died 27 hours later, following a massive hemoptysis.

Autopsy showed a circular defect on the right lateral aspect of the trachea at the level of the bifurcation. This defect was connected with a paratracheal cavity which, in turn, communicated with the lumen of the right main pulmonary artery. Microscopic examination of the aorta showed typical syphilitic aortitis. Stained sections showed slender spirochetes resembling *Spirochaeta pallida* in the media of the pulmonary artery and at some distance from the edge of the defect. The syphilitic lesion in the pulmonary artery was obviously a late tertiary manifestation of syphilis.

Intracranial tumors. A study of 467 histologically verified cases. A. B. Baker. Minnesota Med., St. Paul, 23: 696. Oct. 1940.

Records of intracranial neoplasms which were available from the University of Minnesota were investigated, and 467 that allowed careful histologic study were chosen. This material is believed to offer a fairly accurate picture of the frequency of the various types of tumors. Six cases of gumma were found, all of which occurred in the cerebral hemispheres. Gummas are extremely rare, and in recent years, due to the intensive antisyphilitic therapy, this type of lesion has become a curiosity in medicine and pathology.

DIAGNOSIS

Negative serology in florid secondary syphilis. I. Ciaecio and A. Vadalà. Riforma méd., Napoli, 56: 1027-1031, Aug. 17, 1940.

The authors report the case of a 28-year-old woman in the fourth month of pregnancy with a secondary, papular

syphilitic skin eruption as well as lesions on the mucous membranes of the external genitalia. In the dark-field examination of material obtained from these lesions occasional spirochetes were found. At this time the Wassermann and flocculation reactions for syphilis were negative. Repeat tests were again negative. Two further serologic examinations done at intervals of 4 days were again negative. Three days later the Wassermann reaction was 1 plus and the Meinicke reaction 2 plus. Antisyphilitic treatment, using intramuscular injections of neoiaco, was begun. After the patient had received a total dosage of 4.6 gm. of this drug, the lesions still persisted. She was then given bismuth injections and protein therapy which resulted in complete healing of the lesions. About 2 weeks after antisyphilitic treatment had been started, the Wassermann and Meinicke reactions were both 3 plus.

The authors discuss the theories given to explain this phenomenon of seronegativity in secondary syphilis. They state that they believe it to be due to an abnormal variation of the normal immunobiologic mechanism which characterizes the secondary stage of the disease, that the serologic paradox is due to a deficit of antibody. They cite Rajka's explanation of this pseudonegativity—that the absence of antibody in the circulation may be the result of an insufficient antigenic stimulus, perhaps the result of an unusual localization of spirochetal foci so that these do not stimulate antibody production, or that it may be due to the presence of an inhibitory substance.

"Bubonulus" in lymphogranuloma venereum. Robert Brandt. *Arch. Dermat. & Syph.*, Chicago, 42: 811-813, Nov. 1940.

Three cases of lymphogranuloma venereum are reported, in each of which a circumscribed bubo-like eminence developed on the penis. The lesions were much smaller than a true bubo and, moreover, were not related to lymph glands. The term "bubonulus", as used for circumscribed infiltration around lymph vessels in chancroid, seems to be proper also for

this lesion in lymphogranuloma venereum.

CASE 1. In 1936 the patient, a Negro, had been treated for a chancroidal bubo. In January 1939 he had a penile lesion and swelling in both groins. The test for chancroid and the Frei test were positive. In April he returned to the clinic because of swelling of the penis. A specific Frei antigen could be prepared from the pus aspirated from the bubo. The nature of the bubonulus was also shown by its development during an infection with lymphogranuloma venereum, the considerable time which had elapsed since the previous infection with chancroid, the clinical appearance of the lesion, and the continuous increase in the strength of the Frei reaction.

CASE 2. In March 1939 a Negro presented a typical chancroidal ulcer on the glans penis. The test for chancroid and also the Frei test were positive. The Wassermann test had been positive for a year but no treatment had been given. The sores quickly disappear under sulfanilamide. In February 1940 an eminence developed on the penis, following treatment of 2 other ulcers. The bubonulus became harder and smaller. Sulfanilamide was discontinued and antisyphilitic treatment instituted. In May during treatment with neoarsphenamine new ulcerations developed. The first lesions were chancroid, but the positive Frei reaction and the qualities of the buboes as well as of the bubonulus suggested a diagnosis of lymphogranuloma venereum for the second lesions.

CASE 3. In May 1939 a Negro presented a bubo in the right groin. The glands in the left groin were enlarged. On the inner side of the prepuce was a round well-defined superficial ulcer. The test for chancroid was negative and the Frei test was positive. A prominent infiltration developed behind the ulceration. Sulfanilamide was administered. On July 5 all the lesions were healed. Direct evidence from the pus, the quality of the ulcer, buboes and bubonulus, the cutaneous tests, and absence of previous chancroidal infection proved that the lesion was a part of lymphogranuloma venereum.

Ocular manifestations in venereal lymphogranuloma. V. Barriere and J. May. *Rev. argent. de dermatosif.*, Buenos Aires, 24: 314-330, Pt. 3, 1940.

The authors made a study of the eyes in 120 cases of venereal lymphogranuloma. By means of biomicroscopy they found that in a certain number of cases the nerve endings in the central part of the cornea were increased in number and size. Other findings were ocular hypotension in 87.5 percent of cases, periretinal edema, dilatation and increased tortuosity of the retinal veins, and retinal hypertension. In some patients only edema of the optic nerve papilla was found. These findings were observed in the chronic as well as the acute stages of the disease. The authors believe that the dilatation of the retinal veins and periretinal edema are associated with intracranial hypertension. They found ocular symptoms of the disease in nearly 80 percent of patients with venereal lymphogranuloma.

The responsibility of the physician in correct laboratory diagnosis. Leon S. Lippincott. *Mississippi Doctor*, Booneville, 18: 325-330, Nov. 1940.

When the rapid advance of laboratory methods and the large number of new procedures constantly introduced are considered, it is to be wondered at that so many physicians are able to do as well as they do when sending specimens to laboratories for diagnosis. Lippincott sent questionnaires to the directors of all State laboratories asking what their troubles were in securing proper specimens for accurate laboratory examination. Twenty State laboratory directors sent in replies and Lippincott has listed many of the difficulties encountered. When blood is sent in for serologic tests, the quantity is often insufficient; there is hemolysis caused by contamination; the extremes of temperature have not been noted. Smears for venereal disease examination are made too thick; they consist of superficial exudate. Slides are often put together before the pus is allowed to dry. In submitting chancre

fluid for dark-field examination, the tubes are not adequately sealed; many specimens are too bloody; material is often insufficient. The information regarding the patient should be given in full detail. Often proper information will suggest other examinations than those routinely made, which will prove of great value.

The incidence of heart disease in children with congenital syphilis. Ruth A. Koons and R. W. Kissane. *Urol. & Cutan. Rev.*, St. Louis, 44: 673-674, Oct. 1940.

The problem of the possible relationship of congenital syphilis and cardiac disease in children was approached by the authors from two angles. A group of 100 congenitally syphilitic children was chosen at random from the venereal disease clinic at the Children's Hospital. Detailed histories and careful cardiac examinations were made on each case. In this group one child was found to have heart disease, the lesion being a mitral stenosis. There was, in this case, a history of a superimposed rheumatic infection.

A second group was selected from the cardiac clinic at the same hospital and was comprised of 334 children all of whom were known cardiacs but without reference to rheumatic or congenital etiology. After thorough examination only one of these children was found with the stigmata of congenital syphilis. For this patient a diagnosis of rheumatic heart disease was made with chorea as the etiologic factor in the production of the mitral lesion which was present.

An interesting finding was made on 2 other cases. These were cases of active rheumatic heart disease in which the serum reaction was positive during the period of activity and became negative when rheumatic infection became inactive and without antisyphilitic treatment. (These two cases will be reported later.)

The authors believe that congenital syphilis can practically be disregarded as the etiologic factor in any type of heart disease in children. The association of

rheumatic heart disease and congenital heart disease is incidental.

The serology of syphilis. Reuben L. Kahn. *J. Lab. & Clin. Med.*, St. Louis, 26: 139-155, Oct. 1940.

The serology of syphilis is beginning to enter a highly promising era. From its development during the past 3 decades, it is seen that the serology of syphilis embraces two distinct types of positive reactions. One is essentially an immune serum reaction which apparently is specifically associated with syphilis. The other type of reaction may or may not be associated with immunity; in human beings it most frequently occurs under pathologic conditions, but it is definitely not associated with syphilis.

In the new serology of syphilis, every positive reaction in which there is a question as to its relationship to syphilis will be subjected to special studies, not alone with the verification test but also, should it prove necessary, with all possible supplementary procedures. The serologist then will assume full responsibility for his report just as the roentgenologist, for example, is responsible for his.

Should the serologic reaction be found to be of the general biologic type and unrelated to syphilis, clinicians will not disregard it, but will investigate the reason for this reaction, especially as to whether some pathologic condition is responsible for it. Repeated serologic studies might reveal an increase or a decrease in the potency of the reaction, and these changes might correspond to changes in the pathologic condition. Then again, the studies might reveal, in some cases, a tendency toward positive serologic reactions in the apparent absence of pathologic conditions.

The new serology of syphilis will thus lead not only to more dependable laboratory diagnosis in syphilis, but also to the study of the significance of those reactions not associated with this disease. A positive serologic reaction in the diagnosis of an asymptomatic case will first of all require the "typing" of the reaction

to determine whether it is syphilitic or general biologic. This determination may necessitate repeated serologic studies, considering that a person who shows no signs or symptoms of syphilis is to be diagnosed as syphilitic or as free from syphilis. The increased dependability of the serologic diagnosis of syphilis should remove objections against routine blood testing.

No change in Wassermann reaction from sulfanilamide. Queries and minor notes. *J. A. M. A.*, Chicago, 115: 1569, Nov. 2, 1940.

Query: Can a successful Wassermann test be made on a patient with a rash due to medication with sulfanilamide? Answer: As far as evidence is available there is no reason to believe that therapy with sulfanilamide or its derivatives produces changes in or reversals of the Wassermann reaction. In the course of a large experience no difficulty has been experienced in obtaining correct interpretations of the Wassermann reaction in cases of toxic dermatoses which had been produced by the administration of sulfanilamide.

Studies of the transmissibility of syphilis. The infectiousness of the vaginal secretions and menstrual blood of syphilitic women. Harry Pariser. *J. Invest. Dermat.*, Baltimore, 3: 375-400, Oct. 1940.

By means of a wire loop, specimens for dark-field examination were taken from the cervix and vagina of the patients under study. Mucoid secretion was removed by suction. The cervix and vagina were carefully examined for any lesions. All secretions were injected directly into the testicles of rabbits. From a total of 30 untreated syphilitic women examined by this method, the vaginal secretions of 7 produced syphilis in animals. Five of these 7 women showed local cervical lesions. The 6th "positive" result was obtained from the menstrual blood of a woman with secondary syphilis who had no local cervicovaginal

lesions. The 7th "positive" result was produced from a pregnant woman with early secondary syphilis who had no visible open lesions. The blood serologic tests for syphilis in the rabbits gave high sensitivity ratings, but also produced a definite percentage of nonspecific positive serologic results.

The conclusions reached by the author from these studies are that virulent *Spirochaetae pallidae* are discharged by the syphilitic woman into the vagina in the presence of local lesions. In the absence of such lesions, they are discharged only through the menstrual blood of the early syphilitic or from a cervix which appears abnormal. Infectiousness through the vagina is periodically recurrent rather than continuously present in the syphilitic woman and depends upon the presence or absence of local lesions. The physiologic secretions are not infectious.

In this series, infectious cervical relapse was found to have occurred at least 6½ years after definite onset of the disease. No data can be given as to the absolute end-point or the frequency of cervical relapse.

Biologic false positive serologic tests for syphilis. III. A suggested method of approach to their clinical study. Joseph Earle Moore, Harry Eagle and Charles F. Mohr. J. A. M. A., Chicago, 115: 1602-1606, Nov. 9, 1940.

The recognition of biologic false positive tests for syphilis is of great importance in view of the increasing use of serologic tests in routine medical practice, in industry, and in premarital and prenatal examinations. It is as thoroughly undesirable to make a diagnosis of syphilis and treat a patient who does not have it as to miss the diagnosis in one in whom it exists. Within 2 or 3 years at least 40 examples of biologic false positive tests, either in normal persons or in those with acute infections of undetermined origin, acute infections of the upper respiratory tract, vaccinia, infectious mononucleosis, rat-bite fever, or typhus fever, have come under the personal observation of the authors.

When a patient has a positive serologic reaction for syphilis but gives no history or shows no physical evidence of the disease, the test should be repeated in order to exclude a technically false positive result. The patient should be questioned most carefully, and a complete physical, including a thorough dermatologic examination, should be carried out. If an exhaustive anamnestic and physical search of evidences of syphilis itself is fruitless, the following procedures may be carried out:

- (1) Take a careful history as to symptoms of some intercurrent infection, serum treatment, or vaccination.
- (2) Make a careful physical examination for evidences of acute infection, with special reference to lymph nodes, spleen, and lungs.
- (3) Make a thorough search of blood smears for malarial parasites.
- (4) Examine blood smears for infectious mononucleosis, as this is a much more common infection than it is usually thought to be.
- (5) Make a blood test for heterophile antibody (the Paul-Bunnell test). This is specific for infectious mononucleosis.
- (6) Determine the sedimentation rate.
- (7) Repeat serologic tests for syphilis by several different technics including both complement fixation and flocculation, at least one of which is quantitatively titrated.
- (8) Repeat serologic test for syphilis in several different laboratories of known excellence in order to rule out all possibility of technical error.
- (9) Perform the Kahn "verification test." Until this test, however, has been confirmed by more investigators, a negative result with it should not be accepted as absolute evidence of the false positivity of other serologic tests.
- (10) Test the patient's serum by complement fixation with spirochetal antigen (the Reiter or Kazan strain of cultured *Spirochaeta pallida*). This test is known as Gaechtgen's "palligen" test.
- (11) Test the patient's serum with wholly nonspecific antigens, such as those prepared from bacteria or from such substances as milk and lecithin.
- (12) Carry out a prolonged serologic follow-up (weeks or months) by a good

quantitative technic, testing the blood at frequent intervals without instituting antisyphilitic treatment. (13) Examine members of the family and sexual contacts. Congenital syphilis may thus be ruled out. (14) Examine the cerebrospinal fluid if a decision cannot be reached earlier. (15) The so-called provocative procedure is, in the authors' opinion, worthless. (16) Withhold antisyphilitic treatment unless and until the diagnosis of syphilis is proved. Such treatment is dangerous and should not be given unless the risk is justified by the actual existence of syphilis.

Amyotrophic lateral sclerosis complicated by syphilis and a leukemic condition. Eli H. Orr. *M. Bull. Vet. Admin., Washington*, 17: 178-179, Oct. 1940.

A patient was admitted to Veterans' Administration Facility, Washington, for dermatitis and a muscular atrophy of the left shoulder girdle which had been noted for the past 15 to 20 years. In 1936 he had had a chancre and subsequently had received antisyphilitic treatment. There was a history of gonorrhea in 1920. The serologic reactions of the blood were positive and of the spinal fluid, negative. Special study suggested that the patient might have a leukemia and that the exfoliative dermatitis was due to the leukemia rather than to arsenicals. Atrophy of both shoulder girdles was present. The neurologic evidences pointed to a combination of anterior horn-cell and pyramidal-tract involvement, the etiology of which could not be determined. Complicating the spinal cord condition was the presence of syphilis and a leukemic condition.

Personal experiences in vascular surgery. A statistical synopsis. Rudolph Matas. *Ann. Surg., Philadelphia*, 112: 802-839, Nov. 1940.

This is a summary of the author's personal experience in the surgery of blood vessels, with special reference to aneurysm, from 1877 to the present.

The author states that it is a well-established fact that aneurysms of the aorta were a relatively negligible factor in the mortality of the southern States before the Civil War, and there was an even smaller incidence in the Negro slave population.

At the Charity Hospital, New Orleans, during the period 1825-31, only two aneurysms were recorded among 15,707 total admissions, or one aneurysm to 7,853 admissions. In the decade 1865-75, there were 65,935 total admissions, of which 63 had aneurysms (1 aneurysm to 1,046 admissions). In the decade 1884-1893, there were 199 aneurysms—143 among white patients (71.86 percent of the aneurysms), and 56 among Negro patients (28.14 percent of the aneurysms). This was a ratio of 1 aneurysm to 312.5 admissions of white patients and 1 aneurysm to 344.8 admissions of Negro patients. During the 27-year period, 1904-1931, a total of 1,027 patients with aneurysms were admitted, or 1:335 surgical admissions, 1:1,166 total white admissions, and 1:329.9 total Negro admissions.

In the 5 years, 1935-39, there were 412 aneurysms among the patients admitted, or 1 aneurysm to 742 total admissions. In this group the ratio was 1 white to 3.5 Negro patients. Of these 412 aneurysms, 90 percent were pathogenic (chiefly aortic); of these, 73.3 percent were Wassermann-positive.

The results of this inquiry show that: (1) Aneurysm as a disease and not trauma, has increased 13 times over its incidence 100 years ago; (2) this increased prevalence is particularly apparent in the Negro population (3½ times more prevalent in Negroes than in white persons); (3) this increased prevalence is due to the vast preponderance of the pathogenic aneurysms of arterial disease (90 percent), while the traumatic aneurysms have gained very little in prevalence in the last 40 years (10 pathogenic to 1 traumatic); (4) fully 75 percent of the pathogenic aneurysms were aortic or central; (5) 73.3 percent of these occurred in Wassermann-posi-

tive subjects; (6) apart from the increased incidence of aortic aneurysms due to roentgenographic studies and greater facilities for diagnosis, there has been an actual increase in the prevalence of the disease, confirmed by post mortem evidence.

TREATMENT

Gonococcal arthritis in women. A study of 30 cases. Joseph B. Salberg and Walter M. Brunet. M. Rec., New York, 152: 294-296, Oct. 16, 1940.

A study of gonococcal arthritis in the female is presented. The theoretical opinions regarding the dissemination of the infection are discussed. The numerous treatment procedures are listed and a plea is made for conservative methods of treatment. The histories of 30 patients are reviewed, and details regarding age, race, occupation, and joints attacked are recorded. The patients were treated by conservative but old methods before the general use of the sulfonamides in gonococcal infections came into vogue.

The 30 patients discussed were treated during the years 1931-38. This number represents an incidence of 1 in 200 diagnosed gonococcal infections in the female. Twenty-six of the 30 were white, 4 were Negroes. The marital status of the patients was as follows: 16 married, 6 single, 5 divorced, 2 separated, 1 widowed. The occupations represented were as follows: Housewife, 13; maid, 3; stenographer, 3; clerk, 2; waitress, 2; saleswoman, 2; unemployed, 5. The average age of the patients was 29 years; the oldest was 50; the youngest was 17 years of age. The tissues involved were: Cervix, 24 cases; urethra, 18 cases; rectum, 12 cases; Bartholin gland, 2 cases. Several patients had more than one organ infected. Extension to the fallopian tubes occurred in 9 cases.

The joints attacked were: Wrist, 7 cases; knee, 4 cases; hip, 1 case; foot, 2

cases; hand, 3 cases; shoulder, knee, and wrist, 1 case; shoulder and wrist, 2 cases; shoulder and foot, 1 case; shoulder and hand, 1 case; shoulder, wrist, and ankle, 1 case; knee and ankle, 2 cases; knee and wrist, 2 cases; knee, finger, and toe, 1 case; foot and wrist, 2 cases. The wrist alone or with other joints was involved in 15 cases.

In 11 of the 30 cases the contacts were investigated and in 2 cases only was an arthritis discovered. This number of patients, while small, may argue against the contention that gonococcal arthritis in sexual partners is caused by a particular strain of the diplococcus of Neisser.

The average length of time these patients were under treatment after the development of the arthritis was 4 weeks. The maximum time patients were observed was 13 weeks and the minimum 2 weeks. Four patients lapsed from treatment within the first 2 weeks; they were making excellent progress when they dismissed themselves. Two patients were hospitalized. One of these received hyperpyrexial treatments, and one patient who refused medical care had an ankylosis of the wrist joint. Twenty patients were carried through their treatment period and tests of cure and were discharged. Two patients were readmitted, one in 4 months and the other in 12 months, with a reinfection and a return of the joint symptoms.

In these cases the therapeutic goal was obviously restoration of function of the affected joint. To accomplish this, two phases of therapeutic procedures were carried out: (1) The treatment of the primary focus, and (2) the treatment of the joint complication. Conservative methods were used such as rest in bed when practical, the use of hot sitz baths, the local application of mild antiseptic solutions and suppositories, and sandalwood oil capsules by mouth. Rectal gonorrhea, which occurred in 50 percent of the cases, was not overlooked. Local treatment was valuable.

The authors state that casts for immobilization are rarely indicated. They relieve pain but often the end result is a

fixed joint. Injections of foreign proteins stimulate antibody formation and accelerate recovery. Relief of pain can be obtained by complete bed rest and the use of salicylates and barbiturates. Intravenous injections of salihexin are valuable in the relief of pain. Heat is comforting, and as soon as the swelling subsides mild active and passive exercise will prevent loss of function. Mixed gonococcal vaccine has been found useful in stimulating the defensive forces of the body, but vaccines are not specific and if too large doses are given all immunity will be destroyed.

Silver acetate for prophylaxis against ophthalmia neonatorum. Arch. Ophth., Chicago, 24: 826, Oct. 1940.

In this letter to the editor a question is raised about the advisability of substituting silver acetate for silver nitrate in the Credé method for the prevention of ophthalmia neonatorum. The writer of the letter states that silver acetate could be supplied in ampules by the State, but the cost would be greater than that of silver nitrate. He asks whether the advantages of the use of silver acetate would be sufficient to justify the difficulties involved in changing the present procedures.

In answer it is stated that with the Credé method it has been customary to use a 2-percent solution of silver nitrate immediately after birth. Silver nitrate, when it breaks down, forms a double silver salt and nitric acid. Silver acetate breaks down into a double silver salt and acetic acid. Acetic acid is said to be less irritating to the eye than nitric acid, while the gonococidal powers of the two agents are equivalent in equal strength. Another objection to the use of silver nitrate is that a solution stronger than 2 percent is likely to be irritating, and the use of strong solutions has resulted in severe damage to the eyes. In contrast to this, silver acetate solution becomes saturated at 1.21 percent, and the saturated solution is not irritating to the conjunctiva. The use of a solution of silver acetate would provide protection against ophthalmia neonatorum equal to that of

a solution of silver nitrate and would avoid chemical conjunctivitis and the possibility of employing solutions too strong to be tolerated.

Silver acetate has been used as a substitute for silver nitrate in some hospitals for several years, but the limited number of demonstrative cases from which conclusions can be drawn is due to the excessive zeal of legislative action. The fact that Pennsylvania requires by authority of the health department (which is equivalent to law) the use of silver nitrate or other approved agents of like character in the eyes of all newborn children makes the experimental use of silver acetate possible only with the permission of the State health department. This means a change of established routine in many hospitals, and the effort is simply not put forth to make these desirable experiments.

Temporary myopia due to sulfanilamide.

J. H. Bristow. Arch. Ophth., Chicago, 24: 799-800, Oct. 1940.

The author reports the case of a woman, 21 years of age, treated with sulfanilamide and azosulfamide (neoprontosil; disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3', 6'-disulfonate) for cystitis. Treatment was begun on February 1, 1940, 15 grains (0.97 gm.) of sulfanilamide being given every 6 hours. On February 3 the symptoms of cystitis had subsided. At this time she complained of malaise. She continued the sulfanilamide for 2 days. On February 5 the drug was discontinued. On February 8 the patient complained of numbness, tingling of the feet, and insomnia. The white blood count at this time was 2,550, and the Schilling count was normal. On March 2 there was a recurrence of the cystitis, and the urine contained 15 to 20 pus cells per high power field. The white cell count at this time was 7,350. Owing to the patient's apparent idiosyncrasy to sulfanilamide following her first attack of cystitis, she was given azosulfamide, 10 grains (0.65 gm.) every 6 hours. She took six tablets on March 2. The fol-

Following morning symptoms of nausea and dizziness developed, with extreme lassitude and marked blurring of distant vision.

Ophthalmoscopic examination revealed a clear cornea, an anterior chamber of normal depth, no iritis, and a clear vitreous. Examination of the fundi revealed no evidence of pathologic involvement of the retinas, retinal vessels, or optic nerve heads. Subjective refraction revealed visual acuity of 20/300 in each eye without correction. The use of a -2.00 sphere combined with a -50 cylinder at axis 90 in the right eye gave vision of 20/15, and a -3.00 sphere combined with a -25 cylinder at axis 145 over the left eye gave visual acuity of 20/15. Muscle balance was normal.

With cycloplegia, the refraction was found to be exactly the same objectively and subjectively as it was with the manifest method. The patient was again seen on March 4, at which time her white cell count was 6,400. On March 5 the count had dropped to 3,250. On March 8 the urine was normal, and the patient had no cystitis. On March 21 the white cell count was 4,050, and the patient had no untoward symptoms. Her visual acuity was 20/15 in each eye without correction. Ophthalmoscopic examination revealed no evidence of a pathologic process in the eyes. The patient has been seen several times since and has no apparent difficulty as the result of her transient myopia.

Ocular manifestations of toxicity of sulfanilamide have been reported in the literature on several occasions, although the pathologic process has usually been confined to inflammatory reactions of the lids and conjunctiva and, in a case reported by Bucy, of the optic nerve. Spellberg reported a case which in some respects paralleled the one reported here, although the pathologic process produced was different.

In the case reported here, the pathologic process present was apparently an edema of the lens, particularly in its anteroposterior diameter, producing a shortening of the focal length of the lens (in other words, a myopic eye). A

change in the refractive index of the aqueous, lens substance, or vitreous due to the presence of the drug in these media need not be considered as a cause of the myopia, since an equal concentration must have been present at the time of the first course of treatment when there was no evidence of myopia. The possibility of a spasm of the ciliary muscle producing an artificial myopia is precluded by the fact that the results of objective and subjective refraction were practically the same before and after cycloplegia was induced. A perfect view of the fundus was obtained throughout the entire period of disability and showed no evidence of pathologic involvement of the nerve head, retina, or retinal vessels. The sudden onset of the myopia, due, presumably, to the rapid swelling of the lens, paralleled the occurrence of the angioneurotic edema found in other allergic states.

Value of tryparsamide in the treatment of atrophy of the optic nerve due to syphilis. H. Sutherland - Campbell. Arch. Ophth., Chicago, 24: 670-680, Oct. 1940.

The author reviews the literature on this subject. He believes that tryparsamide should not be used in the treatment of primary atrophy of the optic nerve. He found in the literature only seven reports (with a relatively small total number of cases) which described the treatment of this condition with tryparsamide without resultant damage to the optic system. In the discussion of one of these seven reports a case was included in which the patient seemed to have been adversely affected by the drug. Only three reports indicated improved vision in a few cases. In practically all other reports covering the majority of cases, the harmful effect of the administration of the drug was maintained. Thus, the considered opinion of the majority of investigators seems to be that the use of tryparsamide in the relatively few cases of tabes (or of paresis of the tabetic type) in which primary atrophy of the optic nerve occurs is not justified in view of its dangerous potentialities.

The author reports the case of a white man, aged 27, who had atrophy of the optic nerve due to tabes dorsalis, and in whom a syphilitic amblyopic process became acute in spite of antisyphilitic treatment. The rate of increasing blindness seemed to be definitely stimulated by the institution of treatment which consisted of intramuscular injections of sodium bismuth iodide and sodium iodide in ethyl glycol. The author states that the commencing form of therapy might be questioned in this case. However, the proper method of treatment for such patients is still undecided.

It has been stated by some investigators that tryparsamide should be given in the presence of primary atrophy of the optic nerve because it benefits active syphilis of the central nervous system. The author says that this is debatable. It might just as easily be contended that arsphenamine should be utilized in a case in which there is marked saccular aneurysm of the aorta or in which there is coronary involvement, because it is the best agent that can be employed for syphilis outside the central nervous system. It must be admitted that the Hérxheimer reaction might have a grave effect on the lesions in question in the preliminary phase of the healing cycle. It is well known that in cases of tertiary syphilis in which the lesions are of long standing and are quiescent the eyes may be adversely affected by the use of arsphenamine.

The author disputes the contention of some investigators that the drug should be used because statistics show that blindness due to primary atrophy of the optic nerve occurs in about 35 percent of untreated or inadequately treated syphilitic persons, whereas only some 2 to 10 percent of persons become blind during treatment with tryparsamide. This contention suggests that tryparsamide prevents the development of blindness sufficiently marked to affect the central visual acuity in about 25 percent of the cases.

The effectiveness of the drug in primary atrophy of the optic nerve is questioned, while its danger is generally admitted.

Aneurysm of the abdominal aorta at its bifurcation into the common iliac arteries. A pictorial supplement illustrating the history of Corinne D., previously reported as the first recorded instance of cure of an aneurysm of the abdominal aorta by ligation. Rudolph Matas. *Ann. Surg., Philadelphia*, 112: 909-922, Nov. 1940.

A Negro woman (a field laborer), aged 28, was admitted to Charity Hospital, New Orleans, October 25, 1922. She had a malignant syphilitic infection with generalized manifestations of 8 months' duration before admission. The generalized manifestations included fever; acute polyarthropathies and myalgias localized particularly in the lumbar portion of the spine, hip, knee, and other joints of the lower extremities; general adenopathy; tibial periostitis; and multiple suppurating syphilids on legs, arm, and body. The Wassermann test was strongly positive. The patient was a helpless and crippled invalid when admitted. Under vigorous antisyphilitic treatment she improved so much that, by December 16, 1922, she considered herself well and was discharged at her own request.

She neglected treatment and relapsed. She was readmitted to the hospital on March 6, 1923. In addition to the arthropathies which crippled her spine, right hip, and other parts of her lower extremities, she had an aortic aneurysm (a sequela to an acute aortitis) which involved both common iliac arteries and the aortic bifurcation. A remittent fever developed ranging from 100° to 104° F., but it finally subsided. The aneurysmal tumor grew visibly and rapidly, with increasing lumbar and radiating pressure pains in the pelvis and lower extremities along the right sciatic and anterior crural tracts. By April 3, 1923, the tumor filled the pelvis, projected far above the iliac crest, and reached the umbilical level. Roentgenograms showed marked erosion of the bodies of the third and fourth lumbar vertebrae, the promontory of the sacrum, and the iliac crests. The diagnosis was then estab-

lished of a leaking aneurysm of the abdominal aorta at the bifurcation, involving both common iliac arteries, with progressive retroperitoneal extravasation.

On April 9, 1923, the abdominal aorta was ligated immediately above the sac with two completely occluding, one-half inch, cotton tape ligatures. The aorta was totally occluded for 9 days following the ligature, during which all pulsation ceased and the peripheral pulses in the femoral and pedal arteries were suppressed. During this period of occlusion, the patient remained in a critical condition from threatened cardiac and pulmonary failure (passive congestion, patchy lobular pneumonia, pulmonary edema), which was relieved only by the yielding of the ligatures sufficiently to allow a small, reduced stream to flow through the ligated segment, thus converting a total atresia into a partial, stenotic occlusion. The yielding or relaxation of the ligatures was not caused by any slipping of the knots but (as demonstrated later at autopsy) by the soaking of the cotton fibers in the tissue juices, and the permeation and erosion of the fibers by giant foreign body cells. The cotton tape ligatures were well tolerated by the tissues and caused no damage to the artery.

The postoperative history, after the 9-day period of complete occlusion, was one of early relief from pain and rapid reduction in the size and activity of the aneurysm; gradual, general improvement in weight and strength under the influence of rest, improved nutrition, and specific medication. However, about April 20, 1924, signs and symptoms of progressive tuberculous infection began to manifest themselves in the cervical lymph nodes and in the lungs. The patient died from tuberculosis on September 10, 1924.

During the 1 year, 5 months and 9 days that the patient survived the ligation of the abdominal aorta, the reduced circulation in the sac, enforced rest, and the extremely low blood pressure that characterized the postoperative period all combined to promote the deposition

of laminated clot and progressive consolidation of the sac. On April 11, 1924, about 1 year after the ligation, the aneurysm had contracted fully 60 percent of its original size, and pulsations could be felt only in small, restricted areas. Three months before the patient's death, the aneurysm had solidified and had lost all of its aneurysmal characters. It had become an inert and symptomless pelvic tumor. The patient died of tuberculosis with her aneurysm clinically cured.

On the mechanism of action of hormone therapy in gonorrhea of childhood.

L. v. Dobszay and M. Varady. Arch. f. Kinderh., Stuttgart, 120: 122-132, Aug. 2, 1940.

The bacteriologic and cytologic composition of the vaginal secretion of 25 infants and 5 small children who were being treated with folliculin was studied daily. Folliculin was given in amounts of 25,000 to 30,000 I. B. U. It was observed that after about 50,000 units had been given the number of pus cells gradually decreased while the number of epithelial cells gradually increased. The bacterial flora, at first consisting of only gonococci, also changed to consist of gram-negative and gram-positive cocci, gram-negative bacilli, and bipolar bacilli. Finally all bacteria and pus cells disappeared and only epithelial cells could be seen. Only rarely did Döderlein's bacilli reappear spontaneously.

The glycogen content of the epithelial cells was studied with the Best method. After about 50,000 U. of folliculin had been administered, the formerly glycogen-free epithelial cells were found to contain glycogen in amounts which increased with continued administration of the hormone. By means of the Wohlgemuth procedure no glycolytic ferment could be demonstrated in the vaginal secretion of untreated gonorrhea patients. Since leukocytes contain abundant diastase, the authors explain the absence of glycolytic action in gonorrheal secretion as being due to an as yet unknown biologic inhibitory factor. As the vagina returns to normal under hormone therapy, glyco-

lytic ferment reappears resulting in the splitting of glycogen and an acid reaction of the vaginal secretion.

It was observed that if response to hormone therapy did not occur after 150,000 I. B. U. had been administered, further hormone therapy did not improve the results obtained in these cases. Inoculation of Döderlein's bacilli into the vagina was used as a test of cure; if these bacilli persisted in the vagina, it was considered as a sign of cure.

Both in acute and chronic cases, the initial dose of folliculin was 25,000 I. U. injected intramuscularly. This dose was repeated several times at intervals of 4 to 6 days. After about 75,000 to 100,000 (occasionally 150,000) U. had been given, and only epithelial cells could be demonstrated in the vaginal secretions, Döderlein's flora (obtained from the vagina of 6- to 8-day old, healthy infants), was inoculated into the vagina. As soon as this flora had been found to be established in the vagina (6 to 8 days) two "stabilizing" injections of 25,000 U. each of folliculin, given a week apart, were injected. After a rest period of 3 to 4 weeks the same procedure was repeated. All of the patients were cured with 2 courses of this kind.

Since hormone therapy has no effect on the frequently occurring concomitant infection of the urethra and rectum, it is advised to supplement it with sulfonamide therapy.

On oral bismuth therapy in syphilis. Its debatable value. P. L. Balliña. *Rev. argent. de dermatosis*, Buenos Aires, 24: 301-313, Pt. 3, 1940.

Three patients with secondary syphilis were given treatment consisting entirely of the oral administration of a German bismuth preparation "bismutrat" over a period of 26, 31, and 35 days respectively. It was impossible, by means of this treatment, either to cure the manifest lesions or to prevent the development of new lesions. The dark-field examination remained positive. As soon as these patients received neoarsphenamine, the lesions healed.

In 2 other patients with secondary syphilis the oral administration of "sobisminol" was equally ineffective therapeutically. These patients received the drug over a period of 3 weeks.

The exact dosage of bismutrat is not given. The only statement made is that 2 tablets a day were given for the first few days and 3 tablets a day thereafter. Of sobisminol, 6 capsules a day were given, except for the first few days when the dosage was 4 capsules a day. Each capsule contained 0.75 gm. of the drug (0.15 gm. of bismuth).

Clinical experience with sulfamethylthiazole. [2(para-amino-benzene-sulfamido)-4-methylthiazole.] Alex E. Brown and Wallace E. Herrell. *Am. J. M. Sc., Philadelphia*, 200: 618, Nov. 1940.

Sulfamethylthiazole was used orally in 106 cases for various types of infections, and the drug seemed to produce satisfactory results in a significant number. This was particularly true of infections produced by *Staphylococcus aureus* and *Diplococcus pneumoniae*, Type I.

Lower motor neurone involvement as a complication led the authors to believe it unwise to use sulfamethylthiazole for mild infections caused by *Staphylococcus aureus*. However, this drug or a related preparation may still find a field of usefulness for the treatment of a fulminating infection such as septicemia which carries an extremely high mortality rate that far outweighs the danger of toxic manifestations from drug therapy.

When used orally, sulfamethylthiazole produced concentrations of the free drug in the blood similar to but somewhat lower than those resulting from the use of sulfapyridine, and a minimal amount of conjugation occurred.

With the exception of the highly important and significant complication of lower motor neurone involvement in 3 cases and of cutaneous eruption in 9, there seemed to be fewer toxic effects than were encountered with the use of sulfapyridine and sulfanilamide. Significant nausea and emesis appeared infrequently. No

serious disturbances resulted in the number of erythrocytes or leukocytes. No decline in the carbon dioxide combining power of the blood was noted. No renal complications occurred except in one case in which acetylsulfamethylthiazole crystals formed in the renal pelvis.

Since this study was completed and recorded, sulfamethylthiazole has been withdrawn from clinical experimental use because of the occurrence of the complication of lower motor neurone involvement.

Use of sulphur-containing compounds, particularly pentothal sodium, in conjunction with sulfapyridine. E. J. Radley Smith. Brit. M. J., London, 2: 488-489, Oct. 12, 1940.

It has been said that sulfapyridine should not be given to a patient if he has recently received pentothal sodium for the induction of anesthesia, and, conversely, that a patient under treatment with sulfapyridine must not be given pentothal sodium. This prohibition may be very inconvenient, and the author believes that it is unnecessary.

He reports the cases of 30 patients who were given both drugs without serious complications.

In April 1940, a soldier was given 1.75 gm. of pentothal (containing 3 grains of sulfur) to induce and maintain anesthesia. The operation was for perforated peptic ulcer, and the peritoneal cavity was found to be full of pus. He was given 1 gm. of sulfapyridine intravenously while still on the operating table. This patient made an amazing recovery in every way. There were no complications which could be attributed to the administration of sulfapyridine and pentothal together.

Shortly after, casualties from France and Belgium began to arrive in large numbers at the hospital in which the author worked. In one convoy there were many cases of gas gangrene and other infections. Sulfapyridine was given to very large numbers of men, and pentothal was given to many of these same men to induce and maintain anesthesia.

At the time of the evacuation from Dunkirk the hospital received several

hundred injured patients within a few days, so that many large dressings, removals of tubes, etc., had to be done in a short time. Not enough portable gas apparatus was available, and the difficulty was met by administering pentothal whether the patients had been given sulfapyridine or not. There were no complications from treatment except the usual nausea and vomiting. There was no cyanosis.

Magnesium sulfate and saline purgatives in general have been forbidden to patients receiving sulfapyridine or pentosil, as such a combination has been thought to cause cyanosis. The author believes this prohibition is unfortunate, because there are certain types of cases in which both drugs are required. He refers particularly to the frequent cases of head injury in which there is both an actual or a potential infection of the brain or scalp and the existence of a state of high intracranial pressure due to edema and congestion of the brain. Such patients may require sulfapyridine to combat infection and magnesium sulfate by various routes for cerebral dehydration. The author states that he has personally dehydrated such patients by the oral and rectal administration of magnesium sulfate during sulfapyridine medication without any untoward effects.

Thus the author believes that patients given sulfapyridine can safely be given pentothal or magnesium sulfate. He questions whether sulfur-producing foods, such as eggs, need be withheld from the very numerous patients given sulfapyridine.

Mapharsen in the treatment of forty patients following arsphenamine dermatitis. Arthur. G. Schoch, Lee J. Alexander and W. E. Long. Arch. Dermat. & Syph., Chicago, 42: 919-932, Nov. 1940.

Summarizing reports of 17 cases from the literature, the authors found that after recovery from severe exfoliative dermatitis following arsphenamine therapy, 1 patient tolerated mapharsen and 10 did not; after recovery from mild

arsphenamine dermatitis 5 patients tolerated mapharsen and 1 did not.

The authors are reporting their study of 40 patients who, after recovery from arsphenamine dermatitis, were treated with small, gradually increasing doses of mapharsen. Their conclusions from this study were: (1) Mapharsen can usually be successfully administered to patients after recovery from arsphenamine dermatitis produced by neoarsphenamine, provided the dermatitis is of lesser severity than severe exudative exfoliative dermatitis necessitating hospitalization. The initial dose recommended is 1 mg. and should not exceed 5 mg. (2) Mapharsen cannot be administered successfully even in minute doses to patients who have recovered from severe exudative exfoliative dermatitis due to neoarsphenamine. In intravenous testing with mapharsen, if attempted, the initial dose should not exceed 0.1 mg. (3) Patch tests with mapharsen (3.3 percent solution) are a more reliable guide to further therapy with mapharsen than are patch tests with neoarsphenamine.

Effects of neoarsphenamine and mapharsen on formed elements of blood. Granulocytopenia following neoarsphenamine therapy in a patient who subsequently received mapharsen without untoward reaction. Norman N. Epstein and Ernest H. Falconer. *Arch. Dermat. & Syph.*, Chicago, 42: 909-918, Nov. 1940.

A brief review of the authors' experiences, reported elsewhere, with thrombopenic purpura following arsphenamine therapy is presented. This review indicates that mapharsen usually will not cause a reproduction of this reaction in patients having this type of blood dyscrasia. A study of 30 patients who tolerated antisyphilitic treatment without untoward reaction indicated that neoarsphenamine caused a diminution in the leukocytes and platelets of the peripheral blood, but that mapharsen is much less likely to produce these changes.

An interesting case of granulocytopenia following neoarsphenamine is described

in detail, with a description of the blood and bone marrow changes. The patient tolerated mapharsen without untoward reaction. The mechanism of granulocytopenia following arsphenamine therapy is shown to be quite different from the development of thrombopenic purpura. With the latter there is no injury to the bone marrow, whereas the granulocytopenic reaction is due to a toxic action of the drug on the granulocytic elements of the bone marrow. The granulocytopenia is similar in some respects to that of the aplastic anemia which follows administration of arsphenamine; both represent an injury to the bone marrow.

These cases indicate that mapharsen is less likely to produce granulocytopenia or thrombopenic purpura than are the arsphenamines and that a cautious trial of this drug is justified for patients in whom either of these reactions has developed after arsphenamine therapy, if the need of arsenic is apparent.

Mobilization of bismuth produced by ammonium chloride. Edward F. Corson, Henry B. Decker and Thomas L. Williams. *Arch. Dermat. & Syph.*, Chicago, 42: 868-873, Nov. 1940.

To maintain adequate therapy effectively regular administration of additional quantities of bismuth is necessary. This leads to retention of the drug in the tissues, and when the preparation is employed over a long period relatively large quantities of retained bismuth are stored in the body. A median retention has been reported of 7.4 percent of the bismuth administered. It seemed desirable to the authors to ascertain whether the retained bismuth could be utilized further and reactivated at least in part. The gradual release of the stored bismuth might be of value in extending the treatment of syphilis without further introduction of bismuth.

The 8 patients chosen for the study had received not less than 40 injections of bismuth salicylate averaging 100 mg. each. The last injection had been received from 4 months to 4 years previously. Roentgenograms of the buttocks

showed heavy deposits of the metal. The patients were given daily doses (30 to 40 grains) of ammonium chloride in compound elixir of pepsin N. F. When bismuth failed to be eliminated, the dose of ammonium chloride was doubled, bringing about prompt effect in a majority of cases. Urinary tests for bismuth which formerly gave negative results gave positive reactions as a result of this medication. The results in each case are shown graphically in a table.

In the discussion Corson says it is the intention to follow up this study by roentgenologic examination of the but-tocks to determine whether there is any appreciable diminution in the size of the bismuth deposits.

The treatment of general paresis with malaria induced by injecting a standard small number of parasites. Paul Hoch, Ernest Kusch and L. T. Coggeshall. *Am. J. Psychiat.*, New York, 97: 297-307, Sept. 1940.

The following study of malaria treatment was carried out on 32 patients with general paresis.

The McCoy strain of *P. vivax* was employed with all patients. The parasites for injection were obtained from a person with active malaria. The infected blood was so diluted that each cc. contained a known number of parasites. A thin blood smear was made from the source patient and this was stained with Giemsa's stain in order to determine the presence and stage of development of the malaria parasite. When the parasites were present in the erythrocytes as young ring forms, a simultaneous parasite and erythrocyte count was made from the patient's blood. Particular effort was made to have young forms of the parasites in order to obviate an early increase in the number of parasites contained in the inoculating medium due to the rupture of sporulating forms. From these counts the number of circulating parasites per cc. of infected blood was calculated. One cc. of infected blood was then withdrawn and mixed with heparin granules to prevent coagu-

lation. Immediately after collection this sample was diluted in a previously obtained sample of citrated normal blood so that 1 cc. of the mixture contained 1 million parasites. The dilutions were then made to contain 1,000, 500, 250, or 100 parasites per cc. according to the number desired. All inoculations were given intravenously and as soon as possible after the counts and dilutions had been made.

The results showed that an extremely small number of *P. vivax* trophozoites (between 100 and 250) is sufficient to induce malaria infections. This number is infinitely smaller than the inoculum in the direct transfer of 1 to 5 cc. of infected blood, which is the usual method. There was also found to be a correlation between the incubation period and the number of parasites used to infect the patient but after clinical manifestations were once apparent, there seemed to be little or no difference in the course of the ensuing disease. This study seemed to indicate that the use of a constant small number of parasites for the induction of malaria in paretics would result in a more constant and predictable onset of infection. The number selected for a standard dosage would vary according to the virulence of the strain of parasites used and would have to be determined by an initial titration.

In the present study 25 patients were inoculated with counted small numbers of parasites. The therapeutic effect upon the paresis of 8 (33 percent) was a remission; 10 (38 percent) improved; 6 (25 percent) showed no improvement; and 1 (4 percent) died. The authors state that these results more closely approach those obtained when infected mosquitoes, rather than massive doses of trophozoites, were used for inoculation.

By using the small number of parasites a gradually increasing prodromal temperature preceding the paroxysms was constantly noted. The paroxysms seemed to be milder and better tolerated than those following inoculation of massive doses of parasites. The patient seemed to be in better physical condition

at the end of the therapeutic course of malaria, although a mild paroxysm does not necessarily mean that the patient has a lower temperature or that the chills are of shorter duration. The temperature and rigor of the individual paroxysms were the same as those observed after any mode of infection.

The authors hope that by keeping the dosage of parasites at a minimum it may be possible to reduce the complications and the mortality rate during treatment without impairing the therapeutic results.

The mode of action of therapeutic malaria. Walter L. Breutsch. Reprinted from *Practical Clinical Psychiatry for Students and Practitioners*. E. A. Strecker and F. G. Ebaugh. Philadelphia, The Blakiston Co., 1940. 5th ed., p. 164-170.

The manner by which therapeutic malaria brings about beneficial results in general paralysis is still a disputed question. Previous to the introduction of the malaria therapy investigation of spontaneously recovered cases showed that they had had an incidental febrile disease, such as typhoid fever. This observation gave rise to the theory that increased temperature, by injuring or destroying the spirochetes, was a fundamental factor of recovery. Experiment and study, however, showed that elevated temperature is only a minor factor of a number of highly complicated phases which make up the *modus operandi* of therapeutic malaria.

During the malaria treatment tissue changes take place in the human organism. The course of general paralysis is modified by increasing the number and activity of the histiocytic or clasmato-cytic cells. They seem to function both as a result of the increased phagocytic activity as well as by the production of immune bodies. The enhanced activity of the mononuclear elements seems to be primarily concerned in resolving the parietic brain lesions (perivascular infiltrations) rather than in destroying spirochetes by the way of phagocytosis. The reactive changes on the endothelial

cells of the brain capillaries also play an important role. Endothelial stimulation of the capillaries of the brain cortex by the malaria plasmodium and, in addition, by the debris of the red corpuscles is thought to be one of the more important phases of the therapeutic effect of the malaria treatment of general paralysis.

Operative treatment of neurotrophic joints. John C. McCanley, Jr. *Urol. & Cutan. Rev.*, St. Louis, 44: 592-594, Sept. 1940.

Approximately 10 percent of tabetics have a neurotrophic joint disturbance, or Charcot's disease. A fair percentage of these cases will become suddenly disabled. A painless, wobbly joint, most often a knee, will be surprisingly serviceable until it finally collapses. It is only then that these patients consult a physician. Some of these patients can be rehabilitated to a worth-while degree if this instability and deformity can be remedied. The general physical status is the first consideration in the matter of therapy. The syphilologist is required to furnish an accurate analysis of the patient in terms of his tabetic state and its trend.

If the patient is to be kept ambulant the forms of treatment are few: (1) The wearing of an external brace. (2) An arthrodesis of the disorganized joint, as a means of internal splintage. The neurotrophic joints of neurosyphilis are mainly those having a weight-bearing function: spine, hip, knee, ankle and foot.

The early diagnosis of a Charcot's joint is obviously an advantage. Occasionally a disabling instability does not develop for many years so that an early fusion would prematurely deprive the patient of a movable joint. While fractures in and about the diseased joint are characteristic of a neurotrophic process they also occur in bony structures not associated with a joint. A not uncommon sequence is that of a second Charcot's joint developing below the site of the original lesion. In 6 cases of operative fusion of Charcot's knees the author reports one failure.

Gonorrhea in the male. Results of treatment with sulfanilamide. P. S. Pelouze, Roger W. Barnes, Anson L. Clark, Oscar F. Fox, Rogers Deakin, Robert H. Onstott, Lida J. Usilton and R. A. Vonderlehr, J. A. M. A., Chicago, **115**: 1630-1633, Nov. 9, 1940.

This is a report of a committee appointed by the American Neisserian Medical Society and the U. S. Public Health Service to evaluate sulfanilamide in the treatment of gonorrhea. Case histories from cooperating clinics were chosen. Those of 1,687 individuals treated with either sulfanilamide, local therapy, or both and to whom no previous treatment had been administered were studied. Since 390 of these patients were followed for less than 15 days, they were disregarded in evaluating the results of treatment. Patients having at least 3 negative 2-glass tests in a 2-week period were classified as having a remission.

Over 60 percent of the 1,687 patients disappeared from observation before they had obtained a remission status. Nearly 45 percent of these disappeared before the 49th day. There were 94 patients who were treated by sulfanilamide only and under observation 15 days or longer. A control group of 332 patients were treated with local therapy alone.

The use of sulfanilamide early in the treatment period materially increased the satisfactory results. With the cases followed between 15 and 19 days after beginning treatment, sulfanilamide plus local therapy proved to be over 6 times as effective as local therapy alone in producing remissions, and sulfanilamide alone was over twice as good as local therapy alone. By the 49th day sulfanilamide plus local therapy had obtained nearly twice as many good results (53 percent) as did either alone. Sulfanilamide plus local therapy produced 30 percent good results within the first month, as compared with 9 percent for local therapy alone.

If the amount of sulfanilamide given was more than 400 grains in 7 days, the results were no better than if less than

400 grains were given in 7 days but more than 400 grains in 21 days. If less than 400 grains was given in 21 days, sulfanilamide plus local therapy was no better than local therapy alone.

The 2-glass test, unsupported by either smears or cultures, while a useful clinical guide, was found to be an unreliable index of satisfactory outcome.

The value of liver extract in cases intolerant to arsenicals, heavy metals, and radiation. George Miller MacKee and Girsch David Astrachan. J. Invest. Dermat., Baltimore, **3**: 409-442, October 1940.

The authors have studied 107 patients in an investigation of the value of liver extracts as a therapeutic or prophylactic agent in cases intolerant to arsenicals, heavy metals, or radiation. The results of their studies are analyzed in 16 tables.

The authors drew the following conclusions: Liver extract is a useful therapeutic agent in some patients suffering from manifestations of intolerance due to arsenicals, heavy metals, or radiation. It is a useful supportive measure in patients with a history of previous intolerance to drugs and in those with low resistance presenting difficult therapeutic problems. The results of the investigation of the prophylactic value in patients intolerant to arsenicals or heavy metals indicate that liver extract may be of some value in preventing or ameliorating pruritus, gastrointestinal disturbances, nephritis, pains in the bones, joints, and in some cases of erythema with or without scaling; it was of no value in preventing nitritoid crises. There were more improved cases among those patients intolerant to arsenicals (58 percent) than among patients intolerant to heavy metals (40 percent), and the best results were obtained (improvement 71 percent) in patients who received the largest number of liver extract injections.

Liver extract was used in some cases as a prophylactic remedy, in others as a therapeutic agent to ameliorate after-effects of existing intolerance to arsenicals. A third group comprised cases in which

no intolerance to any drug was established but which presented potential treatment problems.

Side effects of sulfapyridine. R. Hegglin. *Schweiz. med. Wchnschr.*, Basel, **70**: 881-884, Sept. 14, 1940.

The author divides the side effects produced by sulfapyridine into harmless and serious manifestations. Among the harmless side effects he includes nausea and vomiting, cyanosis, porphyrinuria, anemia, exanthemata (2 to 3 percent among 500 cases treated). The more serious manifestations include the formation of urinary calculi (1 percent of cases) and agranulocytosis.

Hematuria was observed quite frequently. The calculi which are formed have been demonstrated to consist of acetylsulfapyridine which is composed of rectangular crystals arranged in bundles. Mechanical trauma produced by these crystals probably causes hematuria; larger calculi may produce typical renal colic. Patients who develop hematuria under sulfapyridine therapy should be carefully watched, since anuria may develop. This is the result partly of mechanical and partly of reflex changes. Fatal uremia as result of sulfapyridine therapy has been reported to be a particularly frequent occurrence in children. Urinary calculi are formed because of the slight solubility of the drug, and therefore occur most frequently with large dosage. That the solubility of the drug is not the only factor, however, is indicated by one of the author's patients who developed calculi with very small dosage of the drug.

Agranulocytosis is usually the result of very high dosage of sulfapyridine. The agranulocytosis is usually of the toxic type similar to that produced by arsphenamine and usually is observed 15 to 27 days after the administration of sulfapyridine has been stopped. The prognosis is serious but not hopeless. An increase in the number of monocytes in the blood is usually a good prognostic sign.

Inaccurate technic employed in giving intramuscular injections of soluble sulfapyridine (soludagenan) may result in serious injury of the sciatic nerve.

Contribution to the question of dagaenai complications. W. Huber. *Schweiz. med. Wchnschr.*, Basel, **70**: 884-888, Sept. 1940.

The author reports a case of uremia due to sulfapyridine therapy. The patient, a 76-year-old man, developed severe iritis following a cataract operation. Because an infection could not be ruled out, he was given 40 gm. Ciba 3714 over a period of 6 days. Three days after the drug had been discontinued, he developed bronchopneumonia of the left lower lobe of the lung. Ciba 3714 proved ineffective in this condition and the patient was therefore given sulfapyridine. During the course of 4 days, he received 28 gm of the drug. Sulfapyridine was then discontinued because the patient felt ill. During the following night colic developed in the region of both kidneys, associated with the passage of a small amount of urine containing much blood. The next morning there was complete anuria which persisted for 3½ days. Attempts to cystoscope the patient were made on the second day of anuria and again 1½ days later. Reddish, granular masses were removed from the kidney pelvises. Diuresis was finally established. However, the patient died of circulatory failure several days later. Autopsy findings included bilateral pyelonephritis with fibrinous deposits in the kidney pelvises and ureters.

The author points out that when extensive crystallization of sulfapyridine occurs in the urinary tract, diuretic therapy is not sufficient. It is necessary to pass sounds into the ureters. Since these crystals may be deposited in acid as well as alkaline urine, prophylactic alkalization of the urine offers no solution to the problem. Sulfapyridine uroliths cannot be demonstrated roentgenologically.



Prince Albert Morrow, M. D.

EDWARD L. KEYES, M. D.

New York City

THE UNRUFFLED calm, the generous enigmancy of Dr. Morrow it must have been that so impressed me the first day I laid eyes on him. He was well enough known to me from his *System of Genitourinary Diseases and Syphilis*, but search that volume as you will, you can find no word of social hygiene in it. So I was not prepared for what awaited me when I answered the bell that called me to my father's office.

There stood that tall, whiskered, saddened man whose pallor already betrayed the nephritis that was to kill him, though he was not man enough to recognize it. When we were seated Dr. Morrow explained that he had asked my father to urge me to act as secretary to a society he proposed to found, the Society of Sanitary and Moral Prophylaxis.

How I wish today for some memory of what he said and how it was he looked. I do not remember to have been fascinated by him nor what happened except that, to my own surprise, I found myself accepting the offer with alacrity in spite of my father's protests that a moral crusade was none of my business—which was true enough. It was only afterward that I learned how ill-prepared I was to fill an oar in that galley.

Looking back at it now, there must have been some hypnotism in Dr. Morrow's slow speech and solemn manner that was religion, something of that which made John Wesley, as he gazed at the utter-drunk, say, "There but for the grace of God—." My thought at the time was that I wished to broaden my contact with life. Something more than that, though, it must have been that

drew President Eliot and Father Lavelle and Charles Sprague Smith and John Rockefeller, Jr., and Anna Garlin Spencer, and all the others—but that was later.

Why tell of his birth and education? These had left him absolutely sincere and earnestly devoted to his profession. Indeed, he was earnest in everything. When he injured his wrist he became a one-handed golfer, a terror to his friends. His professional duties included not only faithful attendance at his dermatology clinic for the poor but also editor-ship for 6 years of the *Journal of Cutaneous Diseases*. In those latter days when I knew him the gay adventure of youth had gone. He still worked late into the night writing his letters in longhand; not until later would he so much as have Miss Buhler to help him.

Look up Dr. Morrow's writings in the *Index Medicus* and you will find amid a stream of dermatologic papers, no trace of social hygiene until 1903, when he was 57 years old. Today, looking back one sees the stirrings of his conscience, a sense of the disaster which is syphilis insontium, slowly maturing. Here is a list of his "pre-Sanitary-and-Moral-Prophylaxis" writings on the subject:

Syphilis and Marriage (a translation of Fournier's classic), 1880.

Prognosis and Treatment of Syphilis, 1885.

Duration of the Syphilogenic Capacity in Relation to Marriage, 1887.

Letter from the Sandwich Islands; Causes of Depopulation in These Islands; the Demographic Effects of Introduced Diseases, Syphilis, Leprosy, etc., 1889.

In the "System" (1894) he wrote only the chapters on Syphilis of the Skin and on Functional Disorders of the Male Genito-urinary System. Nor does the chapter on Marriage and Syphilis in the "Venereal Memoranda," published also in 1894, show any trace of what was to follow in 1903. In the summer of 1902, moved by what one may believe was the last flicker of love for adventure, he had attended the second Conference of Social and Moral Prophylaxis in Brussels and had himself made a delegate for this country. From that day, barring two minor papers, he wrote no more on dermatology but, during those last 10 diminishing years, lived a life devoted to that which we now call, with what wisp of inherited shamefacedness is left us, "social hygiene." In those 10 years he published 34 documents on the subject, one of which, the book "Social Hygiene and Marriage" (1904), expresses social hygiene as we have it today and will remain as much a medical classic as that volume of Fournier's from which confessedly it sprang.

He was spared the ever-recurring terror that has beset us since 1914. He did not foresee the war during which we were to be staggered by the crude problem of a population suddenly overrun by a somewhat licentious soldiery facing a bevy composed of everything from reckless bootleggers and astute panders to worshipping womanhood; a problem so tense and immediate as to swallow up the calmer aspects of sex education in the more imperative policing of camp areas and personal prophylaxis. But his Social Hygiene Association and his Dr. Snow were there to steady us. Still less did he foresee our present gloom from which no one less sane than he can lead us.

Let us in a few random quotations relive those days so brave and young:

"Two International Congresses for the prophylaxis of syphilis and venereal diseases, in which every civilized country of the world was represented, have been held in the city of Brussels. These deliberations crystallized into the conviction

that the system of reglementation employed in most Continental countries was insufficient as a means of prevention and that the whole subject should be studied anew from a broader standpoint and with special reference to the social conditions involved in the causation of these diseases. Especial recognition was given to the fact that the moral as well as medical issues were involved in the problem of prevention (Morrow, 1904)

"At first glance it might appear that the prophylaxis of these diseases, as of other infectious diseases dangerous to the public health, lies within the province of the medical profession. But experience has shown that this class of diseases cannot be dealt with as a purely sanitary problem, they are not susceptible to the sanitary methods ordinarily employed against contagious diseases. Sanitary science must take cognizance of the cause of disease and especially of the means by which it is spread. The cause of these diseases resides in social conditions which the sanitarian cannot control and their communicative mode cannot be reached by the strong arm of repression.

"In their essential nature they are not merely diseases of the human body, but diseases of the social organism. The problem of their prevention and control involves not only questions of hygiene but questions of morality—questions affecting the most intimate relations of social life. This problem is most difficult and delicate and requires for its solution not only a thorough knowledge of existing evil conditions, but a largeness of ideas and a breadth of view which is not possible to those who look at it from the sanitary side alone. To correct the evil conditions there should be a union of all the social forces which work for good in the community." (Morrow, 1906)

"The ancient conception of disease involved the idea of Divine punishment: Disease was accepted as a retribution of sins committed by the bearer or his ancestors. * * * It was a fashionable (Blackstone, 1794) to say the

ne has the plague, leprosy or syphilis. * * * At a later period syphilitic patients, upon their entrance into the hospitals, were soundly cudgelled and the castigation was repeated on their discharge." (Morrow, 1903)

Dr. Cabanes has interpreted the flogging of genito-infectious patients somewhat differently. Without pretending to be able to decide between them we simply relate what Cabanes believes to have been the medieval point of view.¹

"There was a time when patients with venereal diseases were whipped like galley slaves. This was the preliminary to their admission to hospital and they were whipped again at the end of treatment before they were thrown out into the street. Ambrose Paré who witnessed these cruel scenes, speaks of them without rancor as a custom of times not calculated to scandalize anyone.

"In the mind of the people the whipping was a religious punishment, as necessary as Lent itself to appease the wrath of God, but actually this was not the object of the hospital authorities. They hoped that the majority of patients with venereal diseases, rather than submit to the degradation of a whipping, would prefer to treat themselves and so would not clutter up the wards. * * *

"In 1656 a general hospital was founded by Louis XIV for the care of the poor and one of the regulations excluded beggars with venereal diseases, but a few months thereafter the Pitié, Bicêtre, and the Salpêtrière were filled with syphilitics, so the ancient rules were enforced anew but the prospect of whipping did not check the flood of patients. At the Salpêtrière the wards for prostitutes were full of syphilitics seeking treatment 'who had themselves arrested as beggars though that was not their usual trade'."

"The same thing happened at Bicêtre. The hospital was not open a year 'when the syphilitics were upon them. They

were whipped on admission with the exception of those who contracted the disease in matrimony or in some similar manner, as for example, a nurse from an infant.

"Cullerier, physician to Bicêtre, observes in his History of the Revolution that the system had not been abolished in 1792," [though we may assume that it disappeared soon thereafter].

Our notions of hygiene, as Cabanes remarks, are different from what they were. Today sex information is as widespread among the young as is the knowledge of contraception. This is not to say that sex education worthy of the name is any more widespread than general education, for we know now that the two cannot be divorced. Moreover, the doctrine of the medical secret and its violation by the reporting of genito-infectious diseases no longer worries us as it did Dr. Morrow. The standard of morals among women, too, tends to resemble more closely that of men, but who would have dared prophecy 20 years ago the way that was to come about? And, perhaps most fundamental of all, the attitude of the community toward reglementation is not so markedly more civilized as we should like to see it, though we may still hope that ere the end of the century Mrs. Warren's profession will be less well thought of than it is today. "Times change and we change in them," and it is not quite so true as it used to be that "the more it changes, the more it is the same thing." The one thing that remains constant is man's rebellion to change, yet there is less infectious disease, either above or below the belt, than there used to be.

Sex education, professional and amateur, is wiser and more open than it was. Personal prophylaxis is a large protection for those who do, and those who don't, among the young are less likely to be psychically harmed. The treatment of the genito-infectious diseases is being transferred from the drugstore to the health department.

¹ Moeurs intimes du passé, 6ème série, Paris, p. 369.

Did Dr. Morrow push the world on a bit? I think he did, but I was one of the meager 25 who met that February evening in 1903 at the Academy of Medicine and moved our meeting from Hosack Hall to a smaller room where the shadows we threw would seem more portentous.

Years later, in 1930, Anna Garlin Spencer spoke of Dr. Morrow as no one else could. I quote the uncorrected stenographic report of her remarks at a social hygiene dinner.

"And then we had Dr. Morrow—[and] Sanitary and Moral Prophylaxis, the beginning of the entrance of the medical profession into a great socialized movement—[because of which] we speak with reverence of him. We had what has become now the Educational Division. Beginning with Dr. Prince Morrow we had the Medical Division, the sense born to medical men that they were not merely recipients of private confessions from patients who had never been disturbed by any outer condemnation, but that they were also custodians of race purity and responsible leaders for the kind of life that makes the right family. I look upon Dr. Prince Morrow as a prophet and a priest, using that word priest in the highest sense, a dispenser of idealism organized to work.

"And then we had something else happening. These three things, education, legal and moral protection, and the beginning of the large work of the medical profession was caught up in what? In the greatest crusade of social service, the crusade against preventable disease. It is what was implied in that movement that drew the younger, the more idealistic, of the medical profession around Dr. Morrow. But something else developed: All the great movements of science, all the great adventures in medical research, the joining of the solitary laboratory with the public control of States, for that also came. For a long time it seemed to swallow up all else. I, myself,—I hope I may be understood—have sometimes had to withstand doctors to their face when they seemed to imply that all you needed to have a perfect human being was to

make him soundly well. I have known human beings who are well, who live in a sanitary house and a sanitary town and under conditions that preserve their physical well-being, and they are not worth anything as human beings beside some who may have struggled against some inherited weakness, who rise and fall and rise again in that struggle, but whose spirit is so strong that they are truly human.

"But with the crusade against preventable disease we had, added to the prophet and the priest that was Prince Morrow, a general who marshalled the forces of that great crusade * * *." And she proceeded to the praise of Biggs, for whose name I should certainly substitute that of William F. Snow.

What could be more appropriate than that the last work of Voltaire should have been to launch the dictionary of the French Academy, or that the last work of Morrow should have been to set the matter of this world's approval on sex education? The XV International Congress of Hygiene and Demography, meeting in Washington in 1912, was the first to include this topic. The committee in charge consisted of Thomas M. Balliet, Maurice A. Bigelow, and Prince A. Morrow. During that congress Dr. Morrow lay in hospital in a Washington hotel while his friend and successor, Dr. Snow, dashed to and fro between that room and the meeting.

Dr. William H. Welch was ready with the following resolution:

"Whereas: Both the nations abroad and the American citizens at home recognize and pay tribute to the splendid devotion and services rendered by Dr. Prince A. Morrow in the difficult pioneer work of preparing the people for a knowledge that will enable them to safeguard their homes against influences hitherto unrecognized, misunderstood, or deliberately ignored;

"Be it resolved: That the participants of this section on sex hygiene of the Fifteenth International Congress on Hygiene and Demography consider it a privilege to make public record of their sense of obligation to Dr. Morrow for his con-

ageous and unflinching attitude in the face of difficulties that would have discomfited an ordinary man, and admiration for the achievement that has culminated in the prominent position that education in sex hygiene has commanded in the deliberations of this congress."

Syphilis and Gonorrhea Control

Principles of Case-Finding and Case-Holding

MEDICAL DIRECTOR C. C. PIERCE,

United States Public Health Service

FINDING cases of syphilis and gonorrhea and holding these cases until they are rendered noninfectious and until they have been given adequate treatment is the heart, the core, the mainspring of the entire venereal disease control program. The heart pumps the stream of life through the body but performs no function except to serve the body. The core of a fruit contains the seeds which keep alive the species but cannot exist without the surrounding material. The mainspring of a watch governs the work done by the rest of the mechanism.

Therefore, we should first discuss the part of the venereal disease control program which precedes case-finding, the methods by which we know when a case has been found, and what equipment and facilities are needed to hold the infected person until he has received the greatest possible benefit from treatment. It is important to remember that every "case" is a human being, more or less like ourselves. There should not be too much of a line of demarcation between the infected person and the professional worker. All of us are just people—some are infected and therefore require help and advice; others are prepared by training and experience to give the help that is needed. When we look at the situation in this way, the desired entente cordiale is not hard to establish.

Read at the Tenth New England Health Institute, Hartford, Conn., April 19, 1940.

It was further provided that this minute be suitably engrossed, signed by the chairman and secretary, and presented to Dr. Morrow.

But it was too late. Dr. Morrow died at his home in New York City March 17, 1913.

What is this program which goes before case-finding? First are the efforts to prevent persons becoming infected. There would be no cases to find if this part of the program could be made perfect. The prevention of infection is attempted through educational measures starting in the home, the school, the church, and continuing on through social organizations, service clubs, groups of employees, management, chambers of commerce, professional societies, women's clubs, school teachers, parent-teacher associations, the clergy, and miscellaneous groups of citizens. This educational work to reduce the number of infections that occur should be done by medical, dental, nursing, and other scientific and trained workers prepared for their respective tasks. In fact, many of the groups just mentioned are the best workers in the field when they have become enthused with the possibilities of such service and have acquired the technical knowledge one must possess to pass on to others some modicum of health education.

Second are the powerful agencies of local government and law enforcing bodies which have a definite value of their own in connection with the suppression of prostitution and drunkenness and with the policing of taverns, roadhouses, tourist camps, dance halls, and drinking places where women are employed. These tasks are not to be performed by the health departments but much can be accom-

plished in reducing the number of persons that become infected if health departments will enlist the active support of public officials in the venereal disease control program. These law enforcing agencies are going to become more and more interwoven into the program through requiring the observance of premarital and prenatal examinations required by law in so many States.

Third, there is the question of personal prophylaxis, which is being studied intensively and about which, for obvious reasons, very few workers in this field are willing now to express an opinion.

The next step in providing a background for case-finding is to have trained clinicians and a diagnostic laboratory that carries out dependable microscopic, serologic, and culture procedures. A field worker, an epidemiologist, or a case finder is helpless unless competent clinic and laboratory facilities are available. The quality of such service has improved greatly during the past few years and will continue to do so because of the efforts of health authorities and professional societies to establish State approval of all these diagnostic laboratories.

CASE-FINDING—GENERAL

Various measures have been used and should be continued permanently as dragnet, wholesale methods of locating persons infected with syphilis.

Chicago plan.—A spectacular program of intensive search for infected persons was that conducted in Chicago in 1937 for the purpose of making a thorough-going survey of syphilis. A parade of thousands of people advertised the fact that the city was going to search for hidden cases of syphilis. Thousands of people received letters asking if they would be willing to have their blood tested if their identity was concealed. The Chicago project was of tremendous educational value and differed from all other attempted plans to find syphilis. Two hundred thousand people voluntarily gave their blood for testing and

thus took an active part in the struggle against syphilis. The private physicians in Chicago profited by this work, for hundreds of persons with positive blood tests were sent to them for thorough examination and treatment after the routine blood testing.

Mobile clinic.—Another noteworthy program is the work of the travelling clinic, still going on, which combines case-finding with continued treatment or case-holding. The work which started in southeast Georgia has not only continued but has been adopted by other communities and has possibilities of further development. This plan requires a properly equipped clinic built into an autotrailer, which is manned by trained personnel and which visits various communities. The blood of every citizen in these communities is tested. Those found to be infected are treated until they are rendered noninfectious. When possible repeat visits of the travelling clinic are made until the syphilitic patients have been cured. The work of this clinic has been recorded in the sound film, "Three Counties Against Syphilis," and in magazine articles, as well as in the official records. The mobile clinic unit has been used in eight southern States and has demonstrated that such a unit doubles or trebles the number of cases a clinic unit can find and treat in rural areas where the incidence of syphilis is high.

Hospitals.—Every general hospital should require routine serologic tests of every patient admitted to the hospital or out-patient department. The records have shown the value of this procedure.

One group of hospitals that made blood tests of only those patients suspected of having syphilis found a rate of six-tenths per 1,000 examined. Another group that examined all patients as a hospital routine found 44 cases of syphilis per 1,000 patients. This ratio shows that routine examinations are 73 times as effective as those made only on suspicion.

Routine serologic tests should of course be made on the inmates of all sanato-

riums, hospitals for mental and chronic diseases, asylums, and orphanages.

Industry.—Another effective way to find cases and one that can be continued as a routine matter is the examination of employees in large industrial or mercantile establishments, in railroad and steamship companies, and in any organization which has a number of employees. Small industrial organizations can frequently be interested in the plan of grouping their employees for serologic tests. The executive and clerical employees should be included since anyone can have syphilis.

In making arrangements for examination of persons in industry, not only management but labor should be convinced of the value of the examinations. Certain labor groups have passed resolutions stating that when employers promise to carry out in good faith the venereal disease control program, they will give their hearty cooperation. This means that management must not reject applicants for positions or discharge those already employed who are found to be infected. To make the finding of a positive blood test the criterion of dismissal or rejection from employment would in most cases do grave injustice to the person concerned, to the industry, and to the community. Such action defeats the whole object of the procedure which is to discover cases and bring them under treatment and hold the cases under treatment until they are cured.

It is surprising how many cases are discovered among people who were totally unaware that they had syphilis. The records of the positive cases in an examined group showed that 65 percent of patients with cardiovascular syphilis did not know they had the disease. There must of course be medical follow-up to see that everyone who needs treatment gets prompt and adequate care. The only object of all case-finding work is to prevent the spread of the disease and to cure the patient. Fortunately, syphilitics can be made non-infectious in a short time by proper treatment and apparently can be cured if the treatment is adequate.

Miscellaneous groups.—Many of you, no doubt, recall that about 2 years ago a woman's club gave publicity to the fact that all of their members were going to have serologic tests made to find out if they had syphilis. This was a fine example which these public spirited women set for the general public. Although probably few cases of syphilis were discovered among the members of such an enlightened organization, the action undoubtedly influenced many of the members to require their servants to be examined to find hidden cases of syphilis. Another woman's club arranged for blood tests of their servants, and about 50 percent were found to be positive. Some employers now select for servants known syphilitics who are under treatment because, their disease having been recognized, they have been rendered noninfectious by treatment and have proven their good sense by remaining under treatment. A servant should be discharged for *stopping treatment*, not because he *has syphilis*.

There are other groups for which routine physical examinations, including blood tests and in some cases cultures for gonococci, are highly desirable. Many colleges require such examinations of all applicants for entrance. Even though but a small percentage are found positive and are brought under treatment, the practice has great value as an educational measure. Every college student should be made to realize the seriousness of venereal disease infections and his duty to himself and the community to avoid contracting gonorrhea or syphilis.

It seems perfectly obvious that every local government should provide for the examination and treatment of prisoners infected with gonorrhea or syphilis. Persons confined in reform schools, prison camps, jails, penitentiaries, and other correctional institutions show an infection rate higher than the community average. These persons cannot lapse from treatment before their discharge from confinement. Public funds expended for case-finding and treatment of cases in jail and prisons is money wisely spent.

Legally required measures.—Then we have the enforcement of laws as an aid to discovering unrecognized cases of syphilis and gonorrhea. At the present time, 20 States have laws requiring applicants for marriage licenses to be examined by their physicians and to have a blood test made in an approved laboratory. This sort of requirement is of great value not only in discovering cases of syphilis and gonorrhea but as an educational measure and also in promoting a partnership between doctors in private practice and the local government. The doctor makes the physical examination and furnishes a certificate based on clinical evidence which must be backed up by a blood examination made in a State-approved laboratory, thus establishing a relationship between private practice and official medical work which is highly desirable.

In 19 States there are laws requiring physicians to secure blood tests of expectant mothers which will not only bring to light unrecognized cases of syphilis but make it possible to prevent the birth of syphilitic babies. Unfortunately there are still obstetricians who insist that their patients are in such an exclusive class that routine blood tests are unnecessary. Such an assumption is one of the greatest arguments for compulsory prenatal blood tests.

Carrying out the prenatal examination law will strengthen the partnership between doctors in private practice and the official health workers of the community. The control of syphilis and gonorrhea are medical problems. These diseases cannot be eliminated without the active cooperation of the medical profession, not only the doctors employed at hospitals and clinics and the specialists who now treat syphilis and gonorrhea, but of every doctor in private practice.

Any doctor who fails to secure a diagnosis for a person with gonorrhea or syphilis or who permits a person infected with either of these diseases to lapse treatment without an effort being made to hold the case until cured, is derelict in his professional and community obli-

gations. Most health departments are providing free consultation service, free diagnostic service, free drugs, and free follow-up service to physicians in private practice if they report cases and ask for service. On what grounds, then, can a doctor justify his action if he fails to recognize a case, fails to try to ascertain the source of infection, fails to attempt to prevent his patient from spreading the disease or lets a case lapse treatment before cure? Doctors should be our most productive case-finding and case-holding group.

Dr. Louise Pearce says: "I believe, that if the antisiphilis control campaign is to be completely successful, a special educational effort will have to be undertaken by the medical profession. This, I think, must take two forms. In the first place, the individual physician who plans to include in his practice the care of syphilitic patients will have to have special training to this end. In the second place, it will be necessary for members of the medical profession as a group to appreciate more particularly than has hitherto been the case the essential part they must play in this problem. The measure of success of syphilis control will depend largely upon the degree and persistence of interest in the matter held by the majority of physicians throughout the country."

Dr. Cheever says: "It should be obvious to all who have anything to do with gonorrhea or syphilis that by all odds the most important contact between the patient and the physician is the first one. Frequently, the entire success in the handling of the problem is determined by the first visit. On that may depend the success of a life, or a failure leading to general paresis, or a congenital syphilitic infant. In a busy practitioner's office, regardless of the dozen patients sitting in the waiting-room, the one with suspected syphilis must be considered that day's emergency. The physician's failure to meet this emergency successfully may, years later, cost the patient his life."

Dr. Nathan B. Van Etten, president-elect of the American Medical Association, says: "Getting the patient under treat-

ment involves not only every effort to educate all lay persons about the necessity for treatment of every suspicious sore that does not heal quickly, but it involves also an effort to reeducate every practicing physician to make the correct diagnosis and to institute correct treatment."

Dr. John H. Stokes says: "The private physician must, therefore, as a matter of civic duty, be prepared to examine and collect material for diagnosis of genito-infectious disease, utilizing State-provided facilities for the purpose. He it is, moreover, who must often see on the spot to the initial sterilizing arsenical treatment which removes the individual from the infective contact list. He it is who must carry through the substance of the first interview with the patient, upon which all future cooperation so critically depends. He must as a matter of public health duty initiate that rapport which makes possible in the near future the tracing forward and backward so to speak, of the contacts of the infected person and the course of the disease through the community."

INDIVIDUAL CASE-FINDING

We shall now discuss the details which are essential for a successful program to locate sources of infection and contacts of infected persons encountered in hospitals, clinics, and doctor's offices (if the doctor asks for such service).

Undoubtedly, many of you here today have read the studies on case-finding and case-holding which have been printed in **VENEREAL DISEASE INFORMATION**. The subject matter of these articles is used in the discussion of today and it is recommended that the references listed on the last page be included in your personal file for further study.

The application of epidemiologic principles to the control of venereal diseases is one of the cardinal points in the present national campaign against syphilis. "Find syphilis; treat syphilis" is the four-word summary of the control program.

The question of the method of accomplishment, the relative merits of compulsion and persuasion in inducing patients

to take treatment after they are found, are still much discussed topics among health authorities. It is recognized that the venereal diseases are in a class by themselves. Helen E. Woods has pointed out that the syphilis patient has reason to feel himself in a special class. If a case of typhoid fever or other communicable disease occurs in a home, the necessary isolation of the case has the sympathetic support of the family and neighbors. If, however, a case of syphilis occurs, there is no neighborly sympathy nor will the patient's family attend with the same devotion. In fact, many persons seem to have a great deal of contempt toward persons who have syphilis and it sometimes seems as if the patient and not the disease is the menace to the community.

Compulsory or legal method.—Some States have laws making it the duty of physicians to report to the State department of health by name and address all cases of venereal disease treated by them and to include in the report the name of the probable source of infection. Laws relating to the control of venereal diseases admonish local health authorities to use "all reasonable means" to ascertain the existence of cases of infectious venereal diseases in their respective jurisdictions.

Where such laws have been enacted, it has been the practice of the State department of health to refer immediately to the local health officer concerned any information about the sources of infection given by private physicians reporting cases of venereal disease under their care. This has been interpreted as sufficient legal basis for local health officers to require the examination of persons reported to be spreading syphilis or gonorrhea. Compulsory examination to determine whether or not a suspected person is infected will be used but seldom, compared to the large number of cases that can be persuaded to have an examination made.

In some instances, however, a clinic patient is unwilling or unable to approach his contacts himself, and even specialized clinic personnel cannot accomplish the desired result, that is, find the source of

infection and other contacts of the clinic patient. Usually the persons involved in such cases are clandestine prostitutes, vagrants, itinerants such as carnival company employees and migratory laborers, and occasionally just naturally vicious or especially ignorant persons. Situations of this sort can be handled only by local authorities by conference between the health officer, the prosecuting attorney, and the local judge.

How far the compulsive measures generally applicable in the handling of other communicable diseases can be applied to the control of venereal disease and the relative value of compulsory and voluntary response methods, has been studied by Dr. Norman R. Ingraham and Louise Brown Ingraham. Their New Jersey study showed that the persuasive approach is about 50 percent more productive than the compulsive method.

The persuasive approach method.— Louise Brown Ingraham describes the persuasive approach method of contact-tracing of syphilis. This method requires the tender but direct cultivation of the interest of the patient through friendliness, sometimes through sympathy, often by a generous performance of some personal service. There must be a quick intuitiveness to grasp opportunities, to sense resistance or change in attitude, with a readiness to advance, to retreat, to withdraw. The patient's interest must be constantly maintained by watchful stimulation during the entire interval required for case-finding.

"The worker hunting infectious syphilis learns to temporize while finding out what kind of people his 'prospects' are." Someone has said, "It is just as important to know what sort of a person has syphilis as it is to know that syphilis is the disease a person has."

No two cases present exactly the same problem nor can they be dealt with in an identical manner. The attitude of colored patients is usually that they accept "bad blood" or syphilis as an inevitable affliction, free from disgrace, while white patients look upon their be-

ing afflicted with syphilis with resentment and frequently are suspicious and vacillating in their attitude toward the case worker.

The preparation of the patient for the contact interview is an important procedure. The doctor's examination and a full discussion of the disease from a public health standpoint should always come first.

It is important to waste no time in beginning to identify contacts, exposures and possible sources of infection, but records have disclosed that a higher percentage of patients will cooperate in giving information on subsequent visits to the clinic. Make haste slowly is applicable. Get acquainted before expecting maximum cooperation.

Louise Brown Ingraham says: "Perhaps it is asking too much to expect the syphilis patient to be in any frame of mind to reveal much of his personal experiences on his first harrowing day in the clinic. His anxious fears have been confirmed by the physician's diagnosis; he has run the gantlet of admission routine and has been the victim of painful procedures. With the healing processes of time and arsphenamine, he will be in a more favorable state to discuss the sociological phases of his infection on a later visit to the clinic. First failures do not close the investigation but pave the way to further cultivation of confidence.

"The initial interview is the foundation of all our hopes for success with the individual who has syphilis. It involves an interpretation to the patient which will enable him to accept syphilis as his present illness. It is the basis for his observance of infectious precautions. It is an attempt to forestall his lapse from treatment. It may uncover personal problems that limit his ability to undertake the treatment. It prepares and often completes the necessary arrangements for the examination of contacts. In fact, I suggest that the intelligent interpretation of syphilis may even mean the beginning of effective person to per-

son propaganda for the control of this disease.

"Dr. Gerald Pearson says: 'The development of a positive type of relationship is as important for rapport between the syphilis patient and his physician as in the early stages of psychiatric treatment.' The social worker, as the busy physician's assistant, interviews on a personal level and lays the groundwork for a long-time relationship with each patient.

"It is only fair, and it is also an advantageous mode of approach, to give the patient to understand that he has valid and, in fact, excellent reasons for disclosing his personal experiences. The interpretation of the syphilitic patient's duty to the community should be logical and convincing. The prevalence of syphilis and its unsuspected presence in the community is therefore explained to each patient with understandable simplicity. A feeling of responsibility for warning others and preventing suffering can be developed in most patients. Before the names of exposures are asked for, the patient is convinced of his good fortune in discovering his own illness while it can be controlled and has developed a sympathy for other victims of syphilis ignorant of their infection. The patient is assured of his freedom from guilt in unwittingly exposing others, and thus his confector similarly may be held blameless.

"Effort should be constantly directed toward teaching the patient the manner in which he may seek out his own contacts and persuade them to report for medical examination. The technic just described and readily understood by the majority of patients suggests the use of a similar method in their own activities outside the hospital. If the patient's confidence is won, he willingly trusts the social worker to act through him in letting contacts examined."

She describes how contacts are identified, located, and persuaded to submit to examination. She advises that in discussions with a reported contact the name of the informer be diplomatically con-

cealed as it lessens the possibility of mistaken identity and gives the contact a sense of protection and confidence.

Many workers in the field of syphilis control will agree with her comments that "The method used in the voluntary approach to the infectious syphilis carrier is commended by the evidence of its success."

"Persuasion as a public health practice may be defined as an offer of aid so convincingly extended and so helpfully applied as to earn willing acceptance."

"A small organization for the treatment of syphilis can, through the use of the voluntary approach, obtain a following of faithful patients who will support its chosen public health activities and assist in the spreading of intelligent syphilis propaganda."

In this discussion, case-finding has been considered separately from case-holding, although the two procedures have much in common. If a patient is found by the right method, it will not be difficult to hold the case.

CASE-HOLDING

Case-holding is vital to the public health program for venereal disease control. The technic which has already been discussed with respect to methods of case-finding is applicable to case-holding. The friendly attitude toward the patients who are discovered in a case-finding program establishes the basis for having the infected person remain under treatment until he is pronounced cured, but in addition to this relationship there are other elements that are essential to make case-holding an easier problem.

The clinic where treatment is given has a great deal to do with whether or not a patient will continue treatment. There should be adequate and pleasant waiting-room facilities and sufficient treatment space to give the necessary privacy. Clinics should be located where they are accessible to the patients, and the hours of clinic service should be such that the largest number of patients can visit the clinic with the least incon-

venience to themselves. A venereal disease clinic should, when practicable, be located with other clinics of a hospital or dispensary. This enables the patient to conceal from his associates the type of disease he has and is helpful to the clinic doctor in having consultants available.

Everyone connected with the clinic should bear in mind that the clinic is for the patient and not for the convenience of the doctors, nurses, and other workers. Clinics are treating syphilis, not charity patients. The clinic staff should not take the attitude that they are doing a favor to the patient by treating him, but should make the patient feel that he is discharging his obligation not only toward himself but toward his family and the community in which he lives. Whenever this feeling of responsibility on the part of the patient can be cultivated, that patient will continue treatment until he is discharged by the clinic doctor.

There should be a large enough staff connected with the clinic so that the patient will not feel that he is being hurried through without receiving all the attention and repeated instructions that all patients need. Everybody working in the clinic, the doctors, the nurses, the follow-up workers, the clerks, even the janitor if there is one, should feel a sense of responsibility toward the patients who present themselves for treatment. If the case worker who brought the patient to the clinic is friendly and helpful, but the clerk who makes the records, or the nurse, or anyone else takes an unfriendly attitude, the patient is likely to stay away because he does not like some particular person in the clinic. Crowds, a dull needle, an indifferent doctor, a snippy nurse are excuses good enough to cause patients to discontinue treatment when symptoms subside.

The efficiency of a system that cultivates a friendly attitude toward the patient has been demonstrated in England. Colonel Harrison, who has had charge of syphilis control in England for more than 20 years, said upon the occasion of a visit he made to New York about 2 years ago

that no follow-up system was used in English clinics except for a very few recalcitrant cases. He said their clinic patients kept coming to the clinic until their treatment was completed because they regarded the clinic staff as friends and the clinic as a place where they could always be sure of a cordial greeting and helpful advice.

Many patients need actual service outside the clinic to enable them to keep their appointments. There are many hindrances which must be overcome, such as the care of young children or the lack of transportation, which problems can sometimes be solved by soliciting the help of other agencies.

The difficult type of absentee patient to deal with is one who has been under treatment for some time, and who reasons that if he hasn't been cured by the treatment he has received, he never will be. He has no fear of the disease involving the heart and blood vessels, or the central nervous system. He feels well, and sees no likelihood of anything happening to him. Such cases are a real challenge to any worker, and to convince such a patient of the need for prolonged treatment requires patience, tact, personality, enthusiasm, a thorough knowledge of the disease and an evident sincerity of purpose.

When clinic patients become irregular in attendance they should be followed up at once by one or more of the various methods in use, such as letters, office interviews, home visits, and, if necessary, coercive measures.

Letters.—Many patients can be brought back by a carefully worded letter in which the disease is not mentioned by name. The letter should be personal, not a mimeograph form, sent out in a plain envelope with a post office box number as the return address. If some incident or expression peculiar to the case can be mentioned in the letter, the patient will feel that genuine interest is being shown in his welfare and will respond by returning to the clinic.

Office interviews.—Many patients will comply with a request to come to the office of a worker for an interview if the note is signed by a name familiar to him through previous clinic visits. The office interview gives an opportunity to impart a more thorough understanding of the disease, treatment needs, clinic-patient relationship, and community responsibility. The patient will talk more freely in the office of a worker than he would at home where someone may be listening, interruptions may occur, or questions may be asked by the family after the worker leaves.

Home visits.—Skill in home visiting can be acquired only by experience. Each visit is different from another, as is each patient, in type, nationality, mentality, and peculiarities of each family group.

In connection with home visits, it is essential that the worker keep in close touch with other social and health agencies. There must, of course, be close coordination between the clinic nurse and the field worker engaged in finding cases. If there are in the community trained workers, such as child hygiene nurses, school nurses, case workers of various agencies or Red Cross nurses, who have close contact with the family, a word from any of these may do much to influence the patient's conduct. If there is a generalized public health nursing program under one supervisor with a central office, the problem of utilizing the agencies will be facilitated.

The interviewer must be alert to take advantage of leads the patient gives during the conversation. Miss Cadwallader tells of a young colored girl named Nancy who had been told by the doctor that she would require a year to 18 months of treatment. Nancy said, "Well, how is it Frances has been coming for 3 years?" The worker suggested that she ask Frances if she came every week. Nancy replied that she knew Frances came only when she felt like it. She convinced herself of the need for regularity in treatment more effectively than the worker could have done in an extended conversation.

Coercive methods.—When an infectious patient disregards all efforts to persuade him to take treatment, the local health officer is empowered in most States and large cities to isolate such cases—sometimes in a county or city hospital or by commitment to a State institution. Infectious promiscuous women, vagrants, itinerants and other unfortunates are the only class of patients likely to be handled in this manner. Commitment or other compulsory isolation should be invoked only as a last resort when it is obvious no other course offers any hope of success in preventing the spread of the disease.

This discussion of case-finding and case-holding must close on the note which has been the underlying theme of all that has been said.

Dr. John H. Stokes says that syphilis is not brought to a cure by the injection of drugs into an infected person, but that "the uprooting of the disease from its hold upon humanity is done by the eye, the voice, the understanding and sympathetic spirit without which our much gathering of knowledge is but the unliving dust."

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DIAGNOSIS

The diagnosis and treatment of salpingitis. H. J. Drew Smythe. Practitioner, London, 145: 156-162, Sept. 1940.

The commonest causes of acute salpingitis are gonorrhea and pyogenic infection following parturition. The onset of symptoms of gonococcal salpingitis may coincide in severe infections with the onset of acute urethritis and vulvitis, but it usually comes on 7 to 14 days later, as the result of extension of the infection from the vulval region by douching. This is especially so if a douche nozzle is used which prevents the free escape from the vagina of the fluid used in the douche. Not only is the gonococcus injected into the uterus but other organisms are introduced and, instead of a pure gonococcal infection of the tube, a mixed infection develops, which is much more dangerous. In the common ascending gonococcal infection, the tubal infection is pure and as such is more easily localized and cured and leaves less permanent tubal damage. Pure gonococcal infection gives rise to an acute salpingitis, chiefly affecting the mucosa of the tube, and is always associated with a localized pelvic peritonitis.

Vaginal examination is essential for differential diagnosis. In gonococcal

cases, vaginal examination will show the presence of urethritis and vulvitis and the discharge of pus from the vagina. Pus from the urethra may be expressed and swabs taken for bacteriologic examination.

Gonorrheal cases rarely require operation. The diagnosis of acute salpingitis having been made, the treatment should be rest in bed in Fowler's position, morphine, hot fomentations to the lower abdomen, light diet, mild aperients or an enema if necessary. Sulfapyridine (M & B 693) should be given in high dosage, 6 tablets (3 gm.) at once, followed in 4 hours by 3 tablets and thereafter 2 tablets every 4 hours during waking hours. This treatment should cease after 72 hours. Under such treatment the number of cases requiring operative interference is small.

Carcinoma of the cervix on a gonorrheal basis? E. Leinzinger. *Deutsche med. Wchnschr.*, Berlin, 66: 766-768, July 12, 1940.

The author reports in detail two cases in which there was concomitant gonorrheal cervicitis and carcinoma of the cervix. Both cases occurred in young women with acute gonorrhea whose ages were 25 and 30 years respectively. Cervical biopsies were made from 1 to 5 weeks after the beginning of treatment for gonorrhea because of a persistent erosion of the cervix in spite of treatment. One patient who was treated with X-ray, later had a recurrence and died; the other patient had a radical operation and survived.

The author draws the following conclusions from these observations: (1) It has to be kept in mind that a malignant erosion of the cervix may be accompanied by an acute gonorrheal infection. (2) A biopsy should be made if a cervical erosion does not respond to treatment. (3) Even if the biopsy shows no malignant changes, it has to be kept in mind that the section examined perhaps did not include the neoplasm even though one is present; therefore the

patient should be kept under observation. (4) In the observation of patients following gonorrheal infection particular note should be made of the condition of the cervix.

Transient amaurosis produced by vascular neurosyphilis. Wallace Marshall. Quart. Bull. Northwestern Univ. M. School, Chicago, 14: 192, Winter Quarter, 1940.

A white woman 22 years of age, had periods of temporary blindness associated with marked dizziness, occipital headaches, and coma which began in the fall of 1939. Between the attacks of blindness she had short periods of normal vision.

The pattern of an attack was as follows: (1) A "fogginess" of vision accompanied by a "pulling or burning" sensation in both eyes which was present for about 30 minutes. (2) The patient then rapidly lost color discrimination and the ability to distinguish objects, all within a 10-minute period. (3) Her pupils dilated prior to the onset of these attacks. (4) The vision returned as gradually as it had left her, color discrimination being the last to return. (5) The eyelids then became edematous and discolored, followed by marked lacrimation. During severe attacks, the sister of the patient was unable to awaken her.

The patient's hemoglobin was 34 percent and the erythrocyte count was 2,030,000, when she was first examined. Splenomegaly also was noted. Under iron and liver therapy, her erythrocyte count rose to 2,910,000 and then dropped markedly following another amaurotic episode.

It was discovered that she had previously been treated for syphilis, although blood and spinal fluid tests were negative at this time.

Treatment consisted of thiamine chloride (1 mg. three times daily), together with daily injections of liver extract subcutaneously and iron by mouth. Her headaches and dizziness subsided with this therapy. The transient amaurotic attacks lessened considerably in their intensity and periodicity with potassium

iodide orally and intramuscular bismuth injections. Subsequently she was given mapharsen in 0.04 gm. weekly intravenous injections for 8 weeks. This was followed by weekly injections of tryparsamide. The last attack of amaurosis, one month after the preceding attack, lasted one day, during which she could see objects but had no color discrimination. She subsequently returned to work, and became entirely free from the symptoms of transient amaurosis.

The author comments that early vascular neurosyphilis often presents misleading symptoms. It should be suspected even if the serologic reports of the blood and spinal fluid are negative, especially when unexplained anemia, accompanied by dizziness and headache, is present. Cortical irritation may produce angiospastic phenomena as illustrated by the presence of transient amaurosis.

Headache of syphilitic origin. E. W. Netherton. M. Clin. North America, Philadelphia, 24: 349-364, Mar. 1940.

Headache is a common and distressing symptom which may be caused by many different and unrelated conditions. The possibility of syphilis as an etiologic factor should be considered in cases in which the cause of headache has not been determined.

A thorough examination of a patient who complains of an intermittent, stupefying headache should include a blood serologic test and a cerebrospinal fluid examination. In some cases of late neurosyphilis the serologic reaction and spinal fluid findings may be normal.

Headache of syphilitic origin may occur during the early or late stages of the disease. In the early stages of syphilis, headache is usually caused by syphilitic meningitis. Headache is not an uncommon, but seldom a major symptom of untreated secondary syphilis. Headache which occurs during treatment or following a lapse in inadequate treatment of acute syphilis should be considered seriously as it may be the initial symptom of neurorecurrence. In such a case the

spinal fluid should be examined without delay.

Headache is a frequent symptom of late neurosyphilis of the meningovascular type. It may be the only symptom and may precede by weeks or months the appearance of neurologic signs. The headache is usually severe and is in the frontal or occipital regions. It is usually intermittent and sometimes, but not always, tends to occur at night. The headache of late neurosyphilis is frequently accompanied by one or more symptoms, such as irritability, insomnia, dizziness, nausea, and vomiting. Headache is seldom an important symptom of parenchymatous neurosyphilis, but mental deterioration of variable degree may occur in patients suffering from headache due to late meningovascular syphilis.

Diabetes mellitus and syphilis. A study of two hundred and fifty-eight cases. L. Tillman McDaniel, Herbert H. Marks and Elliott P. Joslin. *Arch. Int. Med.*, Chicago, 66: 1011-1051, Nov. 1940.

The relationship of diabetes mellitus and syphilis occurring in the same patient has for several decades been a frequent subject of discussion by clinicians in all countries. In the latter part of the nineteenth century much was written to the effect that syphilis was either the sole cause or a frequent cause of diabetes mellitus. Many physicians considered diabetes mellitus to be a so-called parasyphilitic disease. The discovery and adoption of serologic tests rapidly dispersed notions of parasyphilitic disease, and the application of laboratory tests for the determination of urine and blood sugar values greatly clarified the situation found in true diabetes mellitus.

Of a total of 15,095 patients with diabetes mellitus observed by the authors, there were only 258 (1.7 percent) with proved evidence of syphilis. The authors analyze the cases of these 258 patients

and review the literature on diabetes and syphilis occurring in the same patient. Nearly 87 percent of these 258 patients had syphilis in the latent stage.

In their review of cases presented in the literature as instances of diabetes due to syphilis, the authors found that practically all of the cases failed to satisfy criteria considered essential for proof of this relationship. The chief factors in the causation of diabetes (heredity positive for diabetes, the state of being overweight, and the age at onset of diabetes) were shown to be the same for diabetic patients with syphilis as for diabetic patients without syphilis.

If "syphilitic diabetes" occurs, the authors believe that theoretically it would most likely be a late manifestation of syphilis occurring in older persons, except in patients with congenital syphilis in whom diabetes is uncommon. Part of the evidence against the relationship of the two diseases is the fact that there is a marked difference between the sexes in the duration of syphilis before the onset of diabetes.

For evaluation of results of antisymphilitic therapy, a diabetic patient with syphilis must be regulated on a constant diabetic regimen. A diabetic patient with syphilis may be given antisymphilitic treatment with the same considerations given to any patient concerning the plan of treatment. To be certain that antisymphilitic treatment has improved or cured diabetes, a case must be followed for years and the condition checked with dextrose tolerance tests.

In this series of 258 patients there was not a single instance of cure of diabetes brought about by optimum antisymphilitic treatment. A patient with the two diseases did not usually appear to have any type of diabetes different from that of the ordinary patient of the same age.

The authors have not been able to recognize the characteristics of such a clinical entity as "syphilitic diabetes."

TREATMENT

Long-term results in the treatment of early syphilis. Paul Padget. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 24: 692-731, Nov. 1940.

In a survey of the literature the author found no satisfactory long-term evaluation of the results of attempts to treat patients with early syphilis by modern methods.

In this article the author analyzes the results of treatment of 551 patients who were treated for early syphilis and then completely reexamined 5 or more years after the termination of their original treatment. The period of posttreatment observation was more than 5 but less than 10 years (mean 7.6 years) in 278 patients, and it was more than 10 years (mean 14 years) in 273 patients. The mean period of observation was 10.8 years for the group as a whole.

The material of this study cannot be considered a random sample because there were more colored women (at the expense of men of both races) than was typical for the clinic from which the patients were drawn. The effort was made to nullify this objection by carefully defining all collateral and conditioning factors.

Comparison of the results of examination at approximately 5 years and at 10 or more years after the original treatment for early syphilis in the 268 patients on whom such comparative examinations were made revealed no patient with a less satisfactory result at the latter examination than at the former. The author considers this fact to be of crucial importance.

Analysis of the final outcome by race and sex revealed no significant difference in the incidence of "cure." Among those who did not achieve "cure," however, neurosyphilis was $2\frac{1}{2}$ times as frequent among the whites. The Negroes of the group had cardiovascular syphilis more often, but the majority of the unsatisfac-

tory results observed in these patients consisted of the persistence of a positive serologic test for syphilis in the blood without other manifestations of the disease. Neurosyphilis was also $2\frac{1}{2}$ times as common among the men as among the women who were not "cured."

Elevation of the blood pressure did not prejudice the prospects of attaining "cure" for the 53 patients who sometimes or always were found to have a systolic pressure above 145 mm. of mercury. The presence of abnormalities in the cerebrospinal fluid was found greatly to reduce the percentage of "cures" attained, and the reduction was in proportion to the severity of the abnormalities.

Among the 534 patients treated, the best results were observed among those who began treatment during the seronegative primary stage, of whom 82 percent achieved "cure." The worst results, only 55 percent of cures, were seen among patients whose treatment was begun in the seropositive primary stage. Among patients with secondary syphilis when treatment began, 68.8 percent were "cured," and in those with early latent syphilis, 58.7 percent were "cured." These differences are, according to the author, probably to be explained on the basis of the immune reaction of the host to the parasite and its disruption by treatment. Emphasis is placed on the fact, that while the incidence of "cure" was higher in the patients who came under treatment with secondary syphilis than among those in the early latent group, the incidence of a persistently positive serologic test for syphilis without other evidence of the disease was more than twice as great in the latter as in the former. Neurosyphilis was more than twice as common among those who began treatment with seropositive primary syphilis as among the others, and it accounted entirely for the increased incidence of unsatisfactory results in this group.

The best results were observed in the patients who began treatment with syphilis of less than 1 month's duration, while

the worst results were seen in those whose treatment began during the second month of the disease.

The development of early or intermediate relapse was found to be of grave prognostic significance. "Cure" was nearly three times as common among those who were not observed to relapse as in those who were, and neurosyphilis was approximately 6 times as common among the latter.

"Cure" was attained by 83.4 percent of the patients whose treatment during the first 6 months was by a continuous system, and this increased to 90.4 percent if treatment during the second 6 months was likewise continuous.

This was in sharp contrast to intermittent and irregular treatment, of which the former was approximately equal to no treatment at all (35.3 percent spontaneous "cure") and the latter was no better. In view of this and other considerations, the author raises the question as to whether, if the patient will not cooperate to receive regular treatment, it would not be better to give no treatment at all rather than irregular or intermittent treatment.

Patients who were given seven to nine injections of arsphenamine during the first 3 months did as well as those who had twice as much treatment scattered over the first 2 years.

The results of this study indicate that serologic testing is not sufficient to determine the true status of patients who were treated for early syphilis in the past, and that complete and painstaking periodic physical examination is likewise essential.

For practical purposes, a patient who has done well for 5 years following the termination of treatment for early syphilis, and at that time has no signs of the disease, may be discharged from further observation.

Diagnosis and treatment of syphilis in infancy and the teen age. F. E. Senear. Illinois M. J., Chicago, 78: 448-457, Nov. 1940.

The author discusses the incidence, diagnosis, and treatment of prenatal

syphilis. He briefly reviews the literature on the subject.

He states that sulfarsphenamine is the drug of choice in infants, in whom the intravenous route, required for the use of arsphenamine, neoarsphenamine, or mapharsen, is difficult to employ. Some authorities advise that a short course of treatment with a heavy metal be given before beginning the use of sulfarsphenamine, but most writers believe that the arsenical should be used at the outset unless the infant's condition is such that it may not survive the initial therapeutic shock resulting from the drug. In such cases from 2 to 3 weeks of treatment with mercury should be carried out before giving the first injection of sulfarsphenamine. In general, small first doses are to be recommended, about 5 to 10 mg. per kilo of body weight, rapidly increasing the dose to a maximum. The maximum for some is 15 mg. per kilo, for others it is up to 25 mg. per kilo. After a series of 8 to 10 such injections weekly a heavy metal may be employed, bismuth subsalicylate (in doses of 2 mg. per kilo) being most favored. All writers insist upon the necessity of prolonged treatment, Moore suggesting a minimum of 40 injections of sulfarsphenamine and an equal number of injections of bismuth or its equivalent in mercury, the first course of heavy metal lasting 4 weeks while succeeding courses of the heavy metal are of gradually increasing length. Some writers have recommended bismarsen as an alternative drug, but the results in general with this drug are not as favorable as with the above combination.

Acetarson, a pentavalent arsenical, has been recommended by some for the treatment of congenital syphilis. Other writers, however, caution that most of the patients treated have not been followed for a sufficient length of time to permit a definite evaluation.

The prognosis of cases of prenatal syphilis depends upon the virulence of the infection in the early days of life and upon the amount of treatment given to both mother and child. The period of greatest danger is the first 6 months of

life. Nearly all infants who show definite clinical evidence of the disease in the first 3 to 4 weeks of life die, while if clinical signs do not appear until 2 to 6 months after birth, the mortality rate drops to about 17 percent. If symptoms do not appear until the age of 7 to 8 months, the mortality rate is only 8 percent. The more severe the symptoms, the higher the death rate. Jones found that of syphilitic children dying during the first year of life, 34 percent had severe lesions and only 5 percent had mild lesions.

Morgan found that if treatment of the prenatally infected child is begun in the early stage, 80 percent will have a serologic cure, while if treatment is commenced before the twenty-eighth month of life, 64 percent of such results will be obtained. If treatment is instituted later, the proportion of favorable results falls to 49 percent.

Smith has found that if treatment is started while the infant is under 6 months of age, it is possible to obtain 83 percent of serologic as well as clinical cures if 50 injections of the drugs are given before the age of 2 years. The response to treatment is proportional to the age at which treatment is begun and to the amount of treatment. Smith also points out that the proportion of cases of serologic fastness is 36.9 percent when treatment is begun during the ages of 2 to 4 years, and it increases to 84 percent when treatment is begun during the 11- to 15-year age period.

All authors point out that prenatally syphilitic children with involvement of the central nervous system do not respond well to treatment, even when serologic reversal occurs, and deterioration may continue in spite of treatment.

Sternberg, in discussing Senear's paper, stated that sulfarsphenamine has been considered a somewhat dangerous drug, particularly because of the high degree of arsenical dermatitis reported as occurring following its use. The great majority of these cases can be anticipated and prevented by a careful examination of the baby each week before treatment, particu-

larly an examination of the skin which will show this up in the preeruptive stages perhaps only as a few scratch marks of the skin. The Wassermann-fast cases, encountered frequently in prenatal syphilis, are not particularly important prognostically. Wassermann-fast cases in prenatal syphilis are found more frequently than in acquired syphilis. The tendency is to treat such patients continuously. Many of them are overtreated, sometimes as much as 4 or 5 years continuously.

Vonderlehr, in discussing Senear's paper, stated that the National Institute of Health of the United States Public Health Service has evidence which may indicate that the sulfarsphenamine manufactured in recent years is a much more chemically uniform and a much more stable preparation than the sulfarsphenamine of 10 or 15 years ago. The Public Health Service is now working on an experiment utilizing sulfarsphenamine and neoarsphenamine clinically to compare the percentage of untoward reactions obtained with the two drugs under identical conditions.

The treatment of syphilis in infancy and childhood. Joseph Yampolsky. Mississippi Doctor, Booneville, 18: 373-377, Dec. 1940.

Since the majority of patients with congenital syphilis are young and many are newborn, it is necessary to answer certain questions before administering the drug: Is the drug safe? Are there painful effects after administration? Can it be diluted so that it can be given safely either intramuscularly or intravenously? From his own experience in treating congenital syphilis, Yampolsky selects neoarsphenamine, sulfarsphenamine, and acetarsone as his choice of drugs.

Neoarsphenamine can be given both intramuscularly and intravenously. When given intramuscularly half of the dose is injected into each buttock. It may be given at room temperature and does not have to be neutralized. It is diluted in the dosage of 0.1 gm. in 1 cc. of distilled water and 0.02 gm. is given

for every 3 pounds of body weight. The author has had success in giving it intraperitoneally. He prefers neoarsphenamine to sulfarsphenamine, which has a tendency to cause abscess formation.

Since there are many discomforts and difficulties in giving hypodermic intramuscular or intravenous injections it is often worth while to try acetarsone orally. The tablets are made into powders, the patient receiving 21 powders weekly, divided into daily doses. The powder is dissolved in water and given $\frac{1}{2}$ hour before feeding. This drug has seemed to be most effective in cutaneous lesions, swelling of joints in young infants, pain on motion of the extremities, condylomas, or general enlargement of the glands. Used in conjunction with bismuth, acetarsone is of great value in the treatment of congenital syphilis. However, acetarsone causes many toxic effects—dermatitis, fever, nephritis, diarrhea, pyelitis, flaccid paralysis, and even death.

The most common preparation of the heavy metals used intramuscularly is mercury salicylate, and the dosage is usually 0.05 grain for every 30 pounds of body weight. Mercury may also be used by inunction. Bismuth may be given in both soluble and insoluble preparations. It should never be given intravenously. Yampolsky has used the aqueous solution of bismuth sodium tartrate in conjunction with acetarsone, the dosage being about $\frac{3}{8}$ grain of metallic bismuth for every 30 pounds of body weight.

The outlook for treatment is much worse in congenital than in acquired neurosyphilis. Of the many methods which have been used of late, it is possible that malaria and fever therapy will supersede all others although Yampolsky does not feel his opinion is of value as yet in this respect.

Four tables are given outlining the recommended treatment for early and late congenital syphilis.

Reactions to tryparsamide. A review of ten years' experience. Herman Beerman and Bertram Shaffer. Brit. J. Ven. Dis., London, 16: 145-165, July-Oct. 1940.

The authors present a review of the records of 113 patients who had been treated with tryparsamide in the Department of Dermatology and Syphilology at the University of Pennsylvania from 1930 to 1939. Of these patients 54 had asymptomatic neurosyphilis; 16 had clinical paresis; 6 had taboparesis (1 with primary optic atrophy); 24 had tabes; 4 had primary optic atrophy; 9 had miscellaneous types of neurosyphilitic involvement and 1 had pemphigus; 9 patients had some optic nerve involvement on admission. One or more systemic reactions to tryparsamide were observed in 16 patients. These included the following cases: Loss of weight, 2; severe nitritoid crisis, 4; nausea and vomiting, 7; itching and/or patchy dermatitis, 4; headache, 1; jaundice, 1; nervousness, 1; neuralgic pains, 1. The type of neurosyphilis apparently had some relationship to the incidence of systemic reactions which was 7 percent for paresis, 18 percent for asymptomatic neurosyphilis, and 13 percent for tabes dorsalis. Sex and color played no apparent role. There was no correlation between the type of reaction to tryparsamide and the number of the injection in the series producing the various reactions. Reaction to previous treatment did not predispose to tryparsamide reactions.

The type of neurosyphilis had a definite relationship to the occurrence of ocular reactions, the incidence being 29.4 percent in asymptomatic neurosyphilis, 25 percent in paresis, 25 percent in taboparesis, 43.9 percent in tabes dorsalis, 25 percent in optic atrophy, and 45.5 percent in miscellaneous types of neurosyphilis. The authors could not explain the high incidence in the miscellaneous group. It was found that patients with normal eyes before treatment had a smaller incidence of

eye complications under tryparsamide therapy than those with eye changes. Out of 103 patients with normal eyes, 81 showed no apparent changes in visual acuity or visual fields during treatment, and 22 had either subjective or objective disturbances of vision. Of the 9 patients with some eye damage, 4 were unaffected while 5 showed progression under tryparsamide treatment. The data showed that the incidence of visual damage is greater in those receiving smaller amounts of treatment prior to tryparsamide than in those receiving larger amounts prior to the use of tryparsamide. Most of the patients received bismuth injections together with tryparsamide. This supplementary treatment appeared to protect rather than to predispose the patient to ocular damage. Although reactions to tryparsamide in general have lately increased somewhat, the authors observed that the number of ocular reactions has not increased during the past 5 years. Although the ocular complications usually occur early in tryparsamide treatment, they may occur late, therefore careful observation of the eyes should be continued as long as this drug is administered.

The authors' data suggested certain defects in the present subjective method of evaluating the toxic ocular effects of tryparsamide on the basis of visual field examination. They point out that a more objective method is needed.

Syphilis. Review of the recent literature. Charles F. Mohr, Paul Padget and Joseph Earle Moore. *Arch. Int. Med.*, Chicago, 66: 1112-1187, Nov. 1940.

The authors selected the material for this article mainly from publications which appeared from July 1939 to July 1940. As in previous reviews they selected their material rigidly. Little attention was paid to reports dealing with comparative serologic studies, and case reports were almost wholly eliminated.

Publications on the following subjects were summarized: History of syphilis.

Spirochaeta pallida. Experimental syphilis. Serodiagnosis of syphilis. Public health aspects. Drugs. Untoward effects of treatment. Incidence of syphilis. Contact investigation. Early syphilis. Latent syphilis. Late syphilis. Cardiovascular syphilis. Neurosyphilis. Syphilis and pregnancy. Congenital syphilis. Syphilis and other diseases.

Subjects of special interest were:

Spirochaeta pallida—staining, distribution of spirochetes in tissue, culture, *Spirochaeta pallida* in blood in early syphilis.

Experimental syphilis—effect of sex hormones on experimental syphilis, immunity in syphilis, experimental fever therapy, tuberculosis in syphilitic rabbits, laboratory animals, serologic tests in syphilitic mice.

Serodiagnosis of syphilis—serologic surveys, quantitative serologic tests, culture spirochetes as antigen in serologic tests for syphilis, daily variation in serum reagin, examination of cerebrospinal fluid, ratio of blood and cerebrospinal fluid reagin content, biologic false positive serologic reactions for syphilis.

Public health aspects—syphilis and national defense, control of venereal disease in the United States, control of syphilis in the South, control of syphilis in Memphis, public interest in venereal disease, syphilis among criminals, syphilis and industry, the teaching of syphilis.

Drugs—spirocheticidal activity of arsenicals in vitro and in vivo, arsphenamine, neoarsphenamine, solusalvarsan, tryparsamide, induced tolerance to arsenic, sobisminol, bismuth in tissues, bismuth and lead, local tolerance of injected bismuth, other drugs, sodium thio-sulfate, vaccine.

Untoward effects of treatment—arsenical dermatitis, erythema of the ninth day, thrombopenic purpura, hepatitis and jaundice, hemorrhagic encephalitis, sodium dehydrocholate as a solvent for neoarsphenamine, reactions to mapharsen, reactions to neoarsphenamine, reactions to tryparsamide, bismuth and hepatic necrosis.

Early syphilis—infectiousness, infectious relapse, osteitis, hepatitis, treatment-resistant syphilis, massive dose method of treatment, supersensitive serologic tests as a guide to cure, the prognosis of early syphilis.

Late syphilis—syphilis of the thyroid gland, traumatic syphilis, syphilis as a cause of elephantiasis of the lip.

Cardiovascular syphilis—incidence, cause of cardiac hypertrophy, association with bacterial endocarditis, association with rheumatic heart disease, association with rupture of the aorta, pathogenesis of aortic insufficiency, aneurysm, aneurysm of the pulmonary artery, intracranial aneurysm, roentgenologic examination in diagnosis of syphilitic aortitis.

Neurosyphilis—diagnosis, Argyll Robertson pupil, optic atrophy, neurogenic bladder, myograms, Charcot joint, hypertrophic pachymeningitis, pseudobulbar palsy, syphilitic polyneuritis, treatment of neurosyphilis, untoward effects of fever therapy, treatment of malaria inoculata.

Syphilis and pregnancy—syphilis as a cause of fetal and neonatal deaths, effect of treatment.

Congenital syphilis—incidence, hereditary ectodermal dysplasia, clavicular sign, changes observed roentgenologically in bones, interstitial keratitis, treatment, physical and mental growth in juvenile dementia paralytica, keratoplasty.

Syphilis and other diseases—tuberculosis, nephritis.

Two hundred and seven references are listed.

Toxic effects of arsenical compounds as administered in the United States Navy in 1939 with special reference to arsenical dermatitis. C. S. Stephenson and Laura T. Anderson. *U. S. Navy M. Bull.*, Washington, 38: 587–597, Oct. 1940.

In 1939, medical officers of the Navy administered 129,295 doses of arsenicals and reported the occurrence of 50 reactions therefrom. Of these reactions 22 were arsenical dermatitis, a ratio of 1 case of dermatitis to 5,877 doses. In 8

cases premonitory signs were noted, which indicates the necessity for careful examination and questioning of each patient before administering an arsenical.

There were 457 doses of bismarsen given during 1939, with no reactions. A total of 14 reactions occurred from administration of mapharsen, a ratio of 1 to 4,671 doses given. From neoarsphenamine, a total of 36 reactions were reported, including 4 fatalities, a ratio of 1 reaction to 1,594 doses, and 1 death to 14,344 doses. There were no reactions from the 943 doses of sulfarsphenamine nor from the 5,120 doses of tryparsamide. The final total of 50 reactions, including 4 deaths, gives a ratio of 1 reaction to 2,586 doses and 1 death to 32,324 doses. For the 15-year period 1925–39, the ratio of reactions is 1 to 1,470 doses, and of deaths, 1 to 31,245 doses.

A cooperative plan for the rapid appraisal of the chemotherapy of gonorrhea in the male. Oscar F. Cox and J. H. Watkins. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 24: 732–736, Nov. 1940.

The American Neisserian Medical Society, in cooperation with the U. S. Public Health Service, has developed a plan, which will shortly be placed in operation, to pool the observations of different clinicians concerning the chemotherapy of gonorrhea. The data thus pooled can be quickly released to physicians interested in the treatment of gonorrhea.

The system is designed to secure from cooperating clinicians reports on individual cases which are being currently treated with sulfonamide drugs. The reports will be made on notification slips, transmitted to a central office where the information will be added to summary data on each case, and at 2-week intervals the results for each drug used will be tabulated and distributed to the cooperating clinicians. The project will be restricted to male cases because it is easier to follow the progress of the disease and to establish criteria of cure in such cases.

The notification slip, to be used by the clinician in reporting progress of each of his cases, will give the identifying numbers and dates of visit, the information desired concerning the drug and amount of dosage, the occurrence of reactions, and the bacteriologic findings.

The statement of results, embodying a separate table for each drug, will show only important essentials in a minimum of detail. The tabulations will summarize by length of treatment-observation period the accumulated data as of a certain date, and (being a current report) will be based on all information received on all cases by the date of release. When sufficient data are accumulated, current tabulations for a drug will be discontinued, and a detailed analysis of the closed series will then be made in order to throw light on those aspects of therapy and outcome which were ignored in the condensed series.

The current analyses of the response to treatment with various drugs will be in terms of: (1) The rapidity with which symptoms subside, (2) the degree to which infections are eliminated as shown by bacteriologic findings, and (3) the frequency of severe reactions.

The information accumulated through this cooperative endeavor will soon become extensive enough to furnish rapid and accurate appraisals of the effectiveness of specific drugs in the treatment of gonorrhea. The tabulations will be available to any clinician who wishes to pool his material on the chemotherapy of gonorrhea in the male by returning a completely filled-out notification slip for every visit of each male patient with gonorrhea. Those clinicians wishing to participate may do so by writing to the Secretary of the American Neisserian Medical Society, 475 Commonwealth Avenue, Boston, Mass., for instructions and notification slips.

Gonorrhea and the sulfonamides. Editorial. P. S. Pelouze. *M. World*, Philadelphia, 58: 615-617, Nov. 1940.

As in the "good old days" the sale of stocks went through what might be called

"the romance stage," then the "shearing stage," and finally the stage of "reality" so, Pelouze says, it is with most of the newer drugs. Even the most highly lauded ones gradually find a place at about one-third of the original vaunted value. He believes so far as sulfonamide drugs are concerned that the romance stage has been passed, and there is now urgent need of getting the scientific facts more widely known. Sulfanilamide has had a most unattractive history because of the loose talk and clinical misinterpretations to which it was subjected. Pelouze feels that because of its lower price sulfanilamide is likely to be used for some time, despite the fact that many think it should be abandoned for the treatment of gonorrhea.

It has been proved that an unfortunately large number of those patients who seem to be cured are, in reality, symptomless gonococcus carriers who can transmit the disease just as surely as can the known treatment failures. An unfortunate feature of this is that when the disease is transmitted the second party usually becomes a totally asymptomatic carrier. So far as sulfanilamide is concerned, it has been shown beyond any possibility of doubt that among patients who are free of symptoms and have had clear urine for 2 weeks, at least 1 out of 3 still has gonorrhea. If, on the other hand, careful microscopic studies have failed to reveal the gonococcus, 1 out of 20 of these patients will still be infected.

There is a decided improvement in the rate of cure with sulfapyridine; many investigators have shown rates of 85 to 90 percent. Even here, however, there occurs a group of asymptomatic gonococcus carriers. Evidence is rapidly accumulating that sulfathiazole is the best of the 3 sulfonamides. It has a rate of cure equal to that of sulfapyridine, and it is far less toxic. But this fact should not tempt one to prescribe it carelessly.

Few physicians ever expected to see such a marvelous advance in the treatment of gonorrhea. But they must not be so blinded by this glory that they fail to keep ever before them the need for the

utmost care in the determination of true cure and the even greater need for the protection of the patient's later sexual life.

Modern chemotherapy of gonorrhea.

H. Fuhs. *Wien. klin. Wchnschr.*, 53: 566-568, July 12, 1940.

On the basis of 2½ years' experience in the treatment of more than 1,200 cases of gonorrhea with sulfonamide preparations, the author concludes that this form of chemotherapy represents a definite advance in the campaign against gonorrhea. They are particularly effective in the treatment of gonorrhea in women and in chronic gonorrhea in men. He has obtained the best results in acute gonorrhea by giving sulfonamide treatment immediately instead of waiting for 2 or 3 weeks as some writers have recommended. The period required for treatment was definitely shortened by the use of these drugs. With careful dosage and discontinuation of the drug as soon as side effects are observed, no serious toxic reactions were noted.

The treatment of anuria due to sulfapyridine calculi. Joseph F. Sadusk, Jr., Levin Waters and Dwight Wilson. *J. A. M. A.*, Chicago, 115: 1968-1973, Dec. 7, 1940.

The symptom complex of hematuria, abdominal pain, and nitrogen retention as a manifestation of sulfapyridine therapy was first described by Southworth and Cooke in May 1939, although the occurrence of hematuria had been previously noted. The seriousness of the pathologic changes which had been demonstrated in animal experiments in the urinary tract became evident with the report of a death from total anuria by Tsao and his coworkers in September 1939.

Detailed histories are given by the authors of 2 cases of complete anuria occurring during sulfapyridine therapy. In the first case (that of a 35-year-old man) the drug was given following operation for a traumatic injury to the head. On the fourth day the patient's urine was

of dark amber color; sulfapyridine was discontinued and fluids were forced. On the fifth day there was complete anuria for 24 hours. A cystoscopy was performed and the excretion was satisfactory. Two hours later the patient pulled the catheters out of place. Dextrose was administered slowly by the intravenous route, but 30 minutes afterward he lapsed into coma and died. The pathologic changes in the upper urinary tract consisted essentially of great tubular and capsular dilatation, marked congestion and vacuolization within the glomerular tufts, and an acute hemorrhagic pyeloureteritis extending into the adjacent renal medullary tissue. The second patient (a 39-year-old man) was being treated for subacute gonorrheal urethritis, prostatitis and arthritis. He was given sulfathiazole for 6 days, followed by sulfapyridine. On the fourth day of this drug he passed dark urine, and this was followed by complete anuria. Upon cystoscopy large irregular concretions were seen completely filling the meatuses. The ureteral catheters were kept in place for 12 hours. Following their removal the patient continued to pass many very small calculi which microscopically were apparently broken-up acetylated sulfapyridine crystals. The patient was discharged in good condition.

Polyradiculoneuritis (Guillain - Barré syndrome) following the use of sulfanilamide and fever therapy. Paul H. Garvey, Nathaniel Jones and Stafford L. Warren. *J. A. M. A.*, Chicago, 115: 1955-1962, Dec. 7, 1940.

The syndrome under discussion is in many respects similar to that generally known as the Guillain-Barré syndrome, which is characterized by motor disturbances, loss of tendon jerks with preservation of cutaneous reflexes, paresthesis with slight disturbances of objective sensitivity, tenderness on pressure of the muscles, little change in the electrical reaction of nerve or muscles, and noteworthy hyperalbuminosis of the cerebrospinal fluid in the absence of cytologic reaction.

The authors discuss 6 cases of polyradiculoneuritis with hyperalbuminosis of the spinal fluid following the use of sulfanilamide and general hyperthermia which they have observed during the past 2 years. Each patient was given 15 hours of fever therapy at 41.5° C. without any unusual complication at the time of treatment or immediately thereafter. In all but one case the neurologic syndrome developed within a period of from 10 to 16 days following fever treatment. Three patients in the series had taken fairly large amounts of sulfanilamide or its derivatives without evidence of toxic manifestations which could be attributed to the drug or the disease. In view of the fact that this neurologic syndrome had never been observed to follow either form of treatment when used alone it was thought perhaps the combination might in some way be responsible. However, a few months later, following a routine 15-hour fever, the same syndrome was observed in 3 patients to whom sulfanilamide had never been given. This seemed to exclude sulfanilamide as a causative agent. Likewise the technic of fever therapy appeared unlikely to be the sole cause. Several features of these cases suggested an infectious (virus) etiology. The latent period between the fever therapy and the development of the neurologic symptoms suggested the incubation period of a virus, and the prevalence of such a virus was indicated by the fact that these cases were all seen during a 2-year period.

The prognosis in these cases has been favorable for recovery. Treatment consisted of the usual therapy for cases of polyneuritis due to other causes.

In the long discussion which followed his paper, several speakers agreed that the syndrome under discussion was probably caused by a virus infection. Bennett said anoxia and thiamine deficiency were more likely causative factors. Jolliffe suggested that the vitamin B requirement of the patients might be doubled by the 10-hour periods of fever therapy and that a deficiency of vitamin B₁ might be a

factor in causing this syndrome. Sands has had an opportunity during the past 4 years of following a group of patients showing a similar symptomatology. In his experience large doses of thiamine hydrochloride made no difference in the speed or the extent of recovery.

Latent gonorrhea of parafrrenal gland.

Case report. Bull. Genitoinfect. Dis., Boston, 17: 3-4, Nov. 1940.

The case reported, from the genito-urinary clinic of the Boston Dispensary, is an illustration of an unusual type of chronic encapsulated gonococcal infection that remained quiescent for almost 1½ years.

The 23-year-old white male patient reported in March 1935 with a urethral discharge of 1 day's duration. A diagnosis of acute gonococcal urethritis was made and treatment with sulfanilamide and anterior permanganate irrigations was begun. In 5 days the patient took 220 grains of the drug without therapeutic effect and the drug was discontinued. It was tried again 1 month later but without success. In May, after 2 weeks of treatment with sulfanilyl-sulfanilamide, smear and culture of the prostatic secretion were negative. A week later treatment was resumed after a diagnosis of parafrrenal (Tyson) gland abscess had been made. The discharge continued for 2 weeks, after which the smear became negative and the gland resumed its normal appearance. In December 1938, the patient was discharged as cured. No manifestations of gonorrhea were observed for 1½ years, when in May 1940 the patient returned, complaining of a slight discharge from the penis. The patient was given sulfa-pyridine for 7 days and the gland was later excised. It is felt that there will be no recurrence in view of the complete removal of the infected sac.

There are several interesting aspects to this case. Sulfanilamide had no effect on the original acute gonococcal urethritis. Although sterilization of the urethra was achieved by sulfonamide therapy, the parafrrenal gland, which was presumably

inaccessible to the drug, was not affected. An asymptomatic, parafrenal gland gonococcus carrier state of almost 1½ years is indicated; reinfection would probably have caused a concomitant acute urethritis.

Gonococcal infections in women. C. J. Van Slyke. *Bull. Genitoinfect. Dis.*, Boston, 3: 1-2, Nov. 1940.

In the early stages of gonococcal infection in women it is relatively easy to make the diagnosis from the history, symptoms, and the finding of gonococci in spreads or in cultures. As the disease becomes more chronic, the value of laboratory procedures declines appreciably, and, therefore, to predicate freedom from gonococcal infections solely on negative spread or culture results is not warranted. Exposure to a known case of gonorrhea, plus clinical evidence of infection, may be a basis for prescribing antigonococcal therapy. The blood complement fixation test is not yet sufficiently established to merit placing reliance upon it in clinical practice.

Sulfapyridine and sulfathiazole are both capable of effecting a high percentage of cures in any stage of gonococcal infection in women. The question of dosage of these compounds is important. The recommended dosage to secure the highest rates of cure with a minimum of reactions is 2.0 gm. per day for 9 to not more than 12 days. Larger doses serve mainly to increase the toxic reactions without appreciably increasing the rate of cure. Concomitant local treatment is usually not indicated. Early discontinuance of therapy should be based only on a consideration of side reactions. The relief of pain and symptoms in complicated cases is usually rapid and complete.

In those cases which fail to be cured, local treatment may be employed for 2 or 3 weeks and chemotherapy then repeated. A cure rate approximating 80 percent is attainable by the therapy recommended.

The criteria of cure whose results have supplied the basis for these recommendations demanded disappearance of purulent discharge together with cessation of clinical evidence of specific infection, evidence of satisfactory recession of adnexal involvement, and negative findings in repeated spread and culture examinations conducted subsequent to chemotherapy.

Therapeutic applications of sulfanilamide and allied compounds. E. M. K. Geiling. *Illinois M. J.*, Chicago, 78: 404-410, Nov. 1940.

The author discusses the therapeutic applications of sulfanilamide, sulfapyridine, and sulfathiazole. In tabular form he presents the following data: (1) Amounts of sulfanilamide necessary to establish effective blood levels (10 to 15 mg. percent) in patients with severe hemolytic streptococcal, meningococcal, gonococcal, pneumococcal, or Welch bacillary infections; (2) amounts of sulfanilamide necessary to establish effective blood levels (4 to 8 mg. percent) in patients with mild or moderately severe tissue infections in which sulfanilamide therapy is indicated; (3) the clinical toxic manifestations of sulfanilamide, sulfapyridine, and sulfathiazole with their time of appearance in the course of therapy; (4) preferred drug (sulfanilamide, sulfapyridine, or sulfathiazole) in the treatment of various infections (sulfanilamide and sulfapyridine seem to be equally effective in gonococcal infections).

The type of examination to which a new drug should be submitted before it is used on humans is as follows: (1) If at all possible, the exact composition (qualitative and quantitative) should be known; or, if that is not obtainable, the detailed method of preparation of the product. (2) Acute toxicity studies on a sufficient number of laboratory animals of different species should be made; studies on one species alone may be very misleading. (3) Chronic toxicity experiments at varying dosage levels and with different species

must be performed in order that any possible cumulative effect of the drug may be noted. (4) Careful and frequent observations of the animals are necessary so that a composite picture of the clinical course is available. (5) Careful pathologic examination of the tissues with appropriate stains is necessary. (6) Effect of the drug on animals with experimental lesions of various important excretory or detoxifying organs, especially of the kidneys and liver, should be studied. (7) The rate of absorption and elimination of the drug, its path and manner of excretion, and the concentration levels in the blood and tissues at varying times after administration must be determined. (8) The possible influence of the presence of certain foodstuffs or drugs should be noted. (9) Careful examinations for idiosyncrasies or untoward reactions should be made.

Some of the pharmacopeial drugs have not been studied along such lines. It is regrettably true that many human lives have been sacrificed by the failure to meet the standards of these preliminary tests and that many more lives will be sacrificed if such standards are not put into effect. Any essential compromise with these requirements will inevitably exact a toll of deaths or injuries among the public. The life and safety of the individual should not be subordinated to the competitive system of drug exploitation.

Methyl sulfathiazole has been withdrawn from further experimental clinical study because of peripheral neuritis which it has at times produced.

Chemotherapy of gonorrhea and its complications with special reference to the cause and prevention of failures.
A. H. Harkness. Brit. J. Ven. Dis., London, 16: 211-231, July-Oct, 1940.

During the last war gonorrhea was a very serious disease, but in this war, due to chemotherapy, there should be few difficulties and it should seldom be necessary for any of the fighting forces to leave their units. Harkness reviews 611 cases of gonorrhea, of which 450 were uncomplicated and 161 complicated. Among the

complicated cases were 52 cases of epididymitis, 8 of acute prostatitis, 54 of acute arthritis, and 5 of gonococcal ophthalmia. There were also 25 cases of primary anorectal gonorrhea. Harkness says he has used all the sulfonamide preparations on the market, but in his opinion M & B 693 and sulfanilamide are therapeutically the most potent and there is little choice between them. After trying varying doses he believes that 1 gm. 3 times daily for 1 week and 1 gm. twice daily for a second week of M & B 693 gives the best results; the dosage of sulfanilamide is 4 grams daily for 4 days and then 3 gm. daily for 2 weeks. He has recently been testing M & B 760 (sulfathiazole) and the results have been excellent.

Among the uncomplicated cases, there were 8 failures due to drug fastness and 5 apparent failures due to residual nongonococcal infections. In 2 cases, owing to the immediate toxic effects of M & B 693 and sulfanilamide, the cure was completed with albucid and posterior lavage. There were 4 immediate gonococcal relapses occurring on the 2d, 3d, 5th, and 9th days after completion of chemotherapy and before the tests for cure had been carried out. Three were cured after a further 7 days' course; the other was suffering from an infection of a para-urethral gland which was destroyed by local treatment. There was only 1 late gonococcal relapse in the series. There were 2 immediate and 4 late nongonococcal relapses; they all followed sexual intercourse and were in all probability primary infections due to nonspecific organisms.

Among the cases with complications, there was a large percentage of failures in the 54 cases of gonococcal arthritis. In 9.4 percent of such cases further joints became involved. The results obtained with the orthodox treatment of the past compare very favorably with those now obtained with the addition of chemotherapy. The sulfonamides have little or no action on a periurethral abscess, an abscess of the prostate, or Cowper's glands until the abscess is drained. Warts are

not influenced in any way by chemotherapy. There were 2 late gonococcal relapses following acute infections of Cowper's gland.

Fundamental principles of treatment of gonococcal infections of women. Robert M. Lewis. Connecticut State M. J., Hartford, 4: 662-663, Nov. 1940.

The majority of gonococcal infections of the urethra and cervix seen in practice can be cured in about 6 months without tubal infection if judiciously handled. Injudicious local treatment can and often does spread the infection to the tubes. Abstinence from alcohol, sexual excitement of every sort, and avoidance of violent exercise are essential. There is no evidence that local applications are curative.

Diagnosis by spreads alone, even in expert hands, is notoriously inaccurate. Positive cultures are of great value, especially after the acute phase has subsided. Single negative spreads and cultures have no significance.

The only curative methods in cases of acute or subacute gonorrheal endocervicitis are the use of sulfonamides in adequate amounts or artificial fever. Inadequate dosage of sulfonamides is not curative but masks the infection. Dosage should be adequate, and the patient must be seen at least every 48 hours. Sulfathiazole, or sulfapyridine, is far more effective and less toxic in adequate dosage than sulfanilamide. If the patient is not improved after 5 days' administration of sulfathiazole or cured after 12 days, the drug should be changed to sulfapyridine, in the same dosage, for 12 days. The reverse procedure may be used if sulfapyridine was first used. In Lewis' experience sulfathiazole has proven less toxic and yields better results than sulfapyridine. The recommended dosage of sulfapyridine or sulfathiazole is 1 tablet, 0.5 gm., every 4 hours for 12 days and no longer.

When given in the recommended doses, Lewis has seen no evidences of toxicity other than slight headache, slight nausea, or malaise. When so given there appears to be no need of carrying out blood concentration tests for other than investigative work. No patient should be discharged as cured until negative spreads and cultures, taken every 2 weeks, have been obtained for 4 months.

The best treatment for gonococcal vaginitis of children is sulfapyridine or sulfathiazole given at 4 hour intervals in doses of $\frac{1}{2}$ grain per pound of body weight. This will probably cure 90 per cent of such cases if continued for 7 to 12 days.

Sulfanilamide treatment of large, multiple chancroid lesions. M. Aberastury. *Semana méd.*, Buenos Aires, 47: 827-829, Oct. 10, 1940.

The author reports the case of a 24-year-old man who gave a history of having had a small erosion of the glans penis in December 1939 which had healed after 6 or 7 days. He was well until February 1940 when a lesion appeared on the left side near the root of the penis. This lesion was the size of a hen's egg and broke down after 12 days. Several other similar lesions appeared in the same area. Dark-field examination of the lesions as well as the blood serologic reactions for syphilis were negative. The Ito-Reenstierna reaction was positive. Treatment consisted of washing the lesions in physiologic salt solution and then covering them with septazine powder. Marked improvement could be observed after 15 days. Auto-inoculation of material obtained from the genital lesion into the left arm resulted in the development of a lesion which was positive for Ducrey's bacillus. At this time oral as well as local chemotherapy was given. After about 3 weeks of this combined treatment the lesions were completely healed.

PATHOLOGY

Clinical observations with sulfathiazole.

A study of 431 patients. Alfred F. Knoll. *M. Rec.*, New York, 152: 364-366, Nov. 20, 1940.

The clinical experiences with sulfathiazole in 431 cases are briefly summarized. Among the patients treated were a few with gonorrheal arthritis and granuloma inguinale, but detailed reports of these cases are not given.

The efficacy of sulfathiazole was found to be equal to, or better than, that of other known sulfonamides in conditions which previously had been susceptible to sulfonamide therapy.

Sulfathiazole has been found to be less toxic than sulfanilamide or sulfapyridine. In these 431 cases, the side effects were minimal in incidence and, in most cases, in severity. No serious effect on the hematopoietic system was seen. Nausea and vomiting rarely occurred, and, when present, were mild. Discontinuance of the drug because of gastrointestinal disturbance became necessary in only one case. Several patients had drug fever, rashes (some of which resembled erythema nodosum), conjunctivitis, and pain in the joints and long bones which promptly subsided with the discontinuance of the drug. One patient had a neurologic syndrome resembling amyotrophic lateral sclerosis which responded well to vitamin E therapy. Hematuria developed in about 20 patients, but gross blood was present in the urine of only two.

There was one death in which sulfathiazole was probably a contributing factor. This was a patient with type V pneumococcus pneumonia of 5 days' duration who was given 6 gm. of sulfathiazole within 12 hours after admission

to the hospital. The daily dosage was cut to 4 gm. on the second day, and to 3 gm. on the third day. It was discontinued on the fourth day because the total sulfathiazole blood level rose progressively from 15.5 mg. percent on the first day to 21.8 mg. percent on the second, and 25 mg. percent on the third day. The nonprotein nitrogen of the blood similarly increased from 28 mg. percent to 208 mg. percent. The patient died on the fourth day. Although the fluid intake during the 3½ hospital days was 3,950, 4,060, and 1,880 cc., the total urine output for 3½ days was only 1,200 cc. (measured) plus an estimated 1,200 cc. voided involuntarily.

At autopsy, extensive gray hepatization was found in both lungs, and a bilateral pyelonephritis of slight degree. The most interesting finding was the presence of numerous, minute, pale yellow, gritty concretions in the medulla of both kidneys which gave the pyramids a stippled appearance. This finding suggested the experimental lesions of urolithiasis medicamentosa due to sulfathiazole reported by Gross, Cooper and Scott and subsequently reported in a human case by Pepper and Horack. However, chemical analysis of the washed, gritty material indicated only a trace of sulfathiazole. It is probable that in the presence of renal damage, with many of the renal tubules already containing concretions, uremia may have been precipitated by temporary blockage of other tubules from sulfathiazole crystals which subsequently dissolved.

Patients who were given sulfathiazole often expressed a desire for more food and admitted a greatly stimulated appetite. Locke recently showed that rabbits given sulfathiazole ate more and gained weight in contrast to rabbits which lost weight during the administration of other sulfonamides. A similar weight increasing effect has been noted with vitamin B (thiamine) which also contains the thiazole linkage.

LABORATORY RESEARCH

Simplified microscopic and macroscopic flocculation tests for the diagnosis of syphilis. Fred Boerner, Charles A. Jones and Marguerite Lukens. *Am. J. Clin. Path., Baltimore*, 10: Tech Suppl., pp. 141-151, Nov. 1940.

The authors describe a microscopic flocculation test and a macroscopic flocculation test for the serodiagnosis of syphilis. These tests are not fundamentally new, but, like most of those now used, are modifications which make the flocculation tests not only simple but more reproducible. The reproducibility of technic is very important, and the lack of it is reflected in the results obtained by the same test in different laboratories.

One difficulty common to most flocculation tests is the preparation of the antigen. Many workers fail to get the desired sensitivity and specificity as recommended by the author of the test. Boerner, Jones and Lukens believe that this difficulty is obviated by the simplicity of the preparation of the antigen in the tests they describe here. There is not a single step in its preparation which requires a great degree of accuracy. For this reason they believe this antigen can be very readily reproduced by others.

In these tests very few doubtful reactions occur because most of the reactions are very definitely positive or negative. This is a distinct advantage, especially to the clinician receiving the report. Because of the short time required for the performance, both tests are very suitable for use as pretransfusion tests in cases where time is at a premium.

The authors have compared these tests with the Boerner-Lukens Wassermann, the Eagle, and the Kline tests. They have been found to be slightly less sensitive than the Kline and to parallel closely the

Eagle and the Boerner-Lukens Wassermann tests. New equipment for the purpose of standardizing the technic is described and shown in photographs. Photographs are presented showing reactions with the tests.

A study of the sera of lepers in quantitative complement-fixation tests for syphilis and tuberculosis. Elizabeth Maltaner. *Am. J. Trop. Med., Baltimore*, 20: 843-848, Nov. 1940.

Although complement fixation tests for syphilis and tuberculosis possess a high degree of specificity as aids in the practical diagnosis of these diseases, questions have arisen regarding their significance in the examination of serums from patients with leprosy. Previous reports uniformly record reactions of serums from active leprosy with tubercle antigens but vary in regard to reactivity in the test for syphilis.

The author examined serums from a series of 47 cases of leprosy from the United States Marine Hospital, Carville, La. These cases included 4 cutaneous, 1 neural, and 34 mixed infections. The antigen used in the quantitative test for syphilis was the cholesteralized boiled alcoholic extract of dried, ether-extracted beef heart tissue that has proved satisfactory both in sensitivity and specificity in routine practice for many years.

In the test for syphilis only 3 of the specimens reacted to a high degree, 2 reacted to a less marked degree, 2 showed a mere trace of reaction, and 2 gave slight reactions that were distinctly atypical in character and routinely would be reported as unsatisfactory. The 35 remaining specimens were negative. One of the patients whose serums reacted to an appreciable degree had a history of chancres a year previously with treatment. In the others, the lesions that were present were explainable on the basis of leprosy alone, although several had had at one time another suggestive signs of syphilis. But one had histories either of venereal exposure or promiscuity. Specimens from all but 1 of the 8 cases had previously

ected in serologic tests for syphilis in another laboratory. Four of the specimens were from neural and 4 from mixed types of leprosy.

Quantitative tests for syphilis and tuberculosis were made with 44 specimens from patients with yaws, secured from Jamaica, B. W. I. All but 3 of the specimens reacted in the test for syphilis, the majority of them to a marked degree.

It was found, therefore, that with purified and accurately standardized antigens and with quantitative methods of testing, it is possible to evaluate more accurately than hitherto the activity of leprosy organisms with the antigens used in the test for tuberculosis and syphilis.

Concentration of arsenic in tissues of experimental animals following intravenous injection of massive doses. B. O. Raulston and H. J. Magnuson. Tr. A. Am. Physicians, Philadelphia, 1940, 55: 255-260.

The work reported was undertaken because of an apparent need for more information concerning the distribution of arsenic in the animal body, especially following the administration of large amounts of arsenicals during relatively short periods of time. The figures presented are based upon the analyses of tissues, blood, urine, bile, and feces obtained from 11 dogs who had received injections of arsenic and 1 control animal who had received 5 percent glucose solution only. Intravenous injections of arsenoxide, 0.4 mg. per kg. of body weight, dissolved in 25 cc. of 5 percent glucose solution were continued for 15 consecutive hours, which allowed 10 doses of the arsenic preparation to be given per day. An animal was sacrificed at the end of 1, 3, and 4 successive days; other animals were kept 4, 8, and 16 days after they had received treatment during 4 successive days. The results of the analyses are obtained in a table.

The arsenic was found to enter brain tissue at a slow rate; low concentration was attained after 4 days of treatment and it disappeared at a slow rate. It was

evident that the concentration of arsenic in other tissues paralleled that in the blood, except in kidney, liver, and bone. The concentration in the kidney and liver reached high levels early because large amounts of arsenic are excreted in the urine and bile.

If the skeletal muscle is considered as representing half the weight of the animal body, the amount of arsenic contained in this was seen to be relatively high throughout the course of treatment. Surprising results were obtained in the concentrations found in the bone. Arsenic accumulated in this tissue rapidly and when treatment was stopped it increased. When the excretion in urine and feces was studied after treatment was stopped, the indications were that arsenic was stored in the bones and then removed gradually by way of the liver and kidneys. The marrow was separated from cortex of bone in a few instances and it was found that the concentration of arsenic was approximately the same in each.

The results obtained in this work indicate that the rate of penetration, the concentration attained, and the rate of disappearance of arsenic from the bone marrow, the liver and the central nervous system are at definite variance with the corresponding conditions in other tissues analyzed. Additional studies, particularly concerning bone, are much needed and are under way.

Prophylaxis of syphilis by locally applied chemicals. Methods of examination, results, and suggestions for further experimental research. Werner Worms. Brit. J. Ven. Dis., London, 16: 186-210, July-Oct. 1940.

The increased incidence of syphilis which accompanies war conditions makes it necessary to think again of all possible means of prevention. Individual local chemical prophylaxis is important although the results obtained have not been uniform either in practice or in experimental research.

The author reviews experimental work in testing the value of a chemical prepara-

tion by examinations in vitro, in vivo, or both, as used by himself, by himself and Schereschewsky, Bessemans, Mahoney, and others. He then discusses the results of experimental work by the various investigators with locally applied prophylactic chemical agents—calomel, mercury perchloride, bisulfate of quinine and mercury, quinine hydrochloride, arsphenamine and bismuth.

Worms believes that the reasons for so many differences in results by different workers lie in the following: (1) The varying intensity of the mechanical injury preceding the inoculation. (2) The size of the injured area. (3) The region chosen for the inoculation. (4) The amount of the chemical substance used. (5) Perhaps also the age of the ointments used, and how long and how intensively they are applied. (6) The relative scarcity of the experiments made; only large series of animals could eliminate errors due to chance which may play a part in any experiment. He says further that detailed research work is still necessary to clear up the problems connected with the prophylaxis of syphilis by locally applied agents. Further studies on the action of mercury in the prevention of syphilis seem to be necessary if, besides the local action, a systematic one occurs, as Mahoney believes. Another point worth investigation seems to be whether or not mercury could be found in the regional glands after the application of Metchnikoff's calomel ointment. Also the numerous experiments in which calomel ointment prevented infection of animals require further explanations.

A rapid simple test for sulfanilamide and its derivatives. Milton M. Hartman. *J. Lab. & Clin. Med.*, St. Louis, 26: 401-405, Nov. 1940.

Hartman reports a test for the sulfanilamide group which is applicable quantitatively to urine and qualitatively to other body fluids. The test commonly in use requires 4 reagents and at least 30 minutes to perform in all its steps. In

Hartman's test the simple addition of para-dimethylaminobenzaldehyde (Ehrlich's reagent) in an acid solution to the tissue fluid produces an immediate bright yellow color. In this test the aldehyde group of the reagent reacts with the free amino group on the benzene ring of the sulfanilamide and its derivatives.

For the quantitative determination of free sulfanilamide, sulfapyridine, and sulfathiazole in urine the Klett-Summerson photoelectric colorimeter with its No. 42 (blue) color filter is used. The results obtained agree exactly with those obtained by the diazotization methods. If a Klett colorimeter is not available there are two other alternatives which give satisfactory results: (1) Match the color obtained with a set of permanent (stoppered) standards prepared from potassium dichromate; (2) compare the color obtained in an ordinary colorimeter with 1:10,000 potassium dichromate.

For quantitative determination of total (free and para-acetylated) sulfanilamide, sulfapyridine, and sulfathiazole in urine: Heat 1 cc. of urine and 1 cc. of 2 normal hydrochloric acid in a covered beaker in a water bath (boiling) for 30 to 60 minutes. Cool. Neutralize to litmus with 2 normal sodium hydroxide. Add water to make up to 200 cc. Run determination as for free compound omitting the hydrogen peroxide, which is no longer necessary.

Comparative studies on the variable toxicity of dagenan (sulfapyridine) and of Ciba 3714 (sulfathiazole) for the erythrocytes of the blood (cell inclusion anemias due to methemoglobin formation). S. Moeschlin and H. Hurschler. *Schweiz. med. Wchnschr.*, Basel, 70: 972-975, Oct. 12, 1940.

The authors have previously reported the finding of inclusion bodies (Heinz's bodies) in the erythrocytes of patients who have been treated with sulfapyridine. These inclusion bodies consist of small, single round bodies located at the periphery of the erythrocyte. These take a

deep stain with vital dyes. They are not related to the so-called reticulocytes. These bodies furnish indirect proof for methemoglobin formation with sulfapyridine therapy, since inclusion bodies occurring in such large numbers have until now been observed only in methemoglobin formation due to nitro-substances and amido-benzenes.

The authors studied the effect of sulfathiazole on the erythrocytes of 120 patients who were being treated with this drug. In none of them could the formation of inclusion bodies be observed and none of them developed definite anemias.

Animal experiments with white mice to whom sulfapyridine was administered showed definite and regular formation of inclusion bodies which could be demonstrated as early as the third to fourth day. No inclusion bodies could be demonstrated in rabbits. Similar experiments with sulfathiazole were negative in spite of large and long continued dosage. There was only a slight increase of reticulocytes and a slight decrease in hemoglobin content. The white blood picture remained unchanged.

As a sign of increased hemolysis due to sulfapyridine, smears obtained from the spleen showed numerous macrophages with abundant, iron-containing pigment and many erythroblasts and erythroblast mitoses, whereas animals treated with sulfathiazole showed only moderate erythropoiesis and few macrophages. The bone marrow findings were less definite in the two groups. It was found that about 2 to 3 days are required for the development of reticulocytes into erythrocytes and about the same time for the inclusion bodies to become visible in the erythrocytes.

These studies show, according to the author, that sulfathiazole has a much slighter toxic effect on the erythrocytes than sulfapyridine, which is probably due to a much less marked methemoglobin formation.

PUBLIC HEALTH ADMINISTRATION

Prostitution as a source of infection with the venereal diseases in the armed forces. Charles R. Reynolds. *Am. J. Pub. Health, New York, 30: 1276-1282, Nov. 1940.*

The author briefly reviews the venereal disease control measures in the United States Army from 1778 to the present. He describes methods used to control prostitution in the vicinity of American military centers in France during the World War.

A recent sign of what may become a serious problem in a national mobilization is revealed in a survey in and about two southern cities during military maneuvers near those places in December 1939 and the early part of 1940. These surveys were conducted by agents of the American Social Hygiene Association and by the United States Public Health Service, engaged in extramilitary sanitation. Prostitution and its accompanying vices seemed to be the chief enterprises in one of these cities which bore the reputation of being the most notorious center of this kind in the South. Among 85 prostitutes examined by health officers, one-third were found to have syphilis, one-half had gonorrhea, and many had both. The situation in the adjoining military station was brought under control only after the most vigorous measures were instituted by the military commander with the assistance of the United States Public Health Service upon request of the Surgeon General of the Army and with the further assistance of the American Social Hygiene Association in cooperation with State and local health and police authorities.

Prostitution must be recognized as a fifth column in the United States, and

it should be dealt with accordingly. Without restraint the forces of prostitution can decimate a military command. Modern life seems to have changed the tactics of prostitution to keep it current with changes in the methods of war. Colonel Dunham has said, "Prostitution has been motorized while the army has become mechanized." In the American Army during the World War there were 357,969 cases of venereal disease among the officers and enlisted men, representing 4,745,415 days lost in the United States and 1,748,067 in the American Expeditionary Forces.

The plan of control today should be one attuned to the requirements of the present military situation and in principle should include: (1) Military measures—continuation of the peace program of prevention, intensified to meet the dangers inherent in a rapidly enlarged Army and Navy; (2) assistance of State and municipal health and police authorities acting under existing statutes and ordinances which in most localities authorize arrest, quarantine, and treatment of prostitutes known to have venereal disease; (3) assistance of the United States Public Health Service in extramilitary sanitation as already authorized by law and now provided by the Administrator of the Federal Security Agency; (4) assistance by an awakened public and such agencies as the American Social Hygiene Association. A joint agreement setting forth the plan of "Cooperation of the United States Public Health Service in Extramilitary Sanitation" has been published.

The author concludes that venereal diseases need not exact a toll from the military forces comparable with past experiences for several fundamental reasons: (1) They are preventable; (2) their prevention is largely an administrative proposition consisting of measures now formulated and standardized through experience in the Army and Navy and

successfully tested during the World War and in the campaign carried on in the civilian population by Federal, State, and local health services; (3) cooperation by the United States Public Health Service, State and local health and police authorities has been more fully developed; (4) an awakened public attitude toward this menace which provides an ally to the military forces and which never before has been adequately mobilized.

Public health in national defense.

W. S. Leathers. *Am. J. Pub. Health*, New York, 30: 1269-1275, Nov. 1940.

Venereal diseases occupy first place among the disabling infections in the military forces of the United States. In the World War the record shows there were approximately 100,000 more new cases of syphilis and gonorrhea in the Army and Navy than there were wounds in battle. A complete account of the devastating effect of these infections in the civil population would present a gloomy and depressing picture.

The appropriation made available by Congress for the administration of the Federal Venereal Disease Control Act in the fiscal year 1940 was \$6,200,000. The discontinuance of the \$4,000,000 appropriation authorized by the Chamberlain-Kahn Act during the last war showed the futility and wastefulness of any sporadic effort for the ultimate control of such infections. No nation or state can afford to pursue a shortsighted policy in not providing adequate funds for a sustained fight against syphilis and gonorrhea. The results already obtained in increased numbers of treatment clinics, in improving serodiagnostic and case-finding procedures, and in arousing universal interest and support are ample proof of the public demand to continue this program until venereal diseases become, like typhoid fever, a negligible health problem.

Relationship of the health of civilians to efficiency of the Navy. With special reference to the venereal disease problem. Charles S. Stephenson. Am. J. Pub. Health, New York, 30: 1291-1296, Nov. 1940.

America must build an effective line of defense against disease, which has always maimed and killed more people than bullets in any war. In order that military forces may be able to carry out their mission it is necessary to "keep as many men at as many guns as many days as possible." Today, it is necessary to keep as many men at as many tools as many days as possible. To accomplish this dual task it is obvious that the health of the civilian population is vital to the efficiency of the Army and Navy.

The greatest single health problem is syphilis, and it is one whose control will not only greatly assist the military surgeon to conserve manpower and effectiveness of the armed forces but also will be of lasting benefit to the civil population.

After the World War, with the demobilization of the military and naval forces, there was a concurrent demobilization of highly trained social hygienists and a drastic reduction of funds from the Federal Government for the control of venereal disease. Men with syphilis who were believed to be noncontagious were discharged from the military services. Many of these men were not adequately treated. Their return to civil life soon resulted in the occurrence of syphilis in communities where, before the war, it was seldom seen. Such a condition must not be allowed to recur.

During the last war, due to the combined efforts of the Army, the Navy, the American Social Hygiene Association, law enforcement officials, and other cooperating agencies, the American Army achieved the lowest venereal disease rate of any military force engaged in that upheaval. Despite that record, there was a shocking loss of manpower. There were 100,000 more new cases of venereal diseases than there were wounds in battle. The Army

lost 6,804,818 sick days. This is equivalent to the absence of nearly 19,000 men for a whole year. The Navy and Marine Corps had 57,146 cases of venereal disease in 1917 and 1918, with a loss of 687,792 sick days. This loss is equivalent to the absence of almost 1,900 men for a year. The above data represents only the reported cases. The number of men who escaped detection and were able to conceal their infections has long been a matter of speculation by serious thinkers on the venereal disease problem. Much of this disease was caused by commercial prostitution.

The civil service personnel of the United States Navy Yards is examined physically prior to employment. Those applicants with active gonorrhea or chancre are rejected. Eligibility for employment is suspended until cure has been effected. Applicants for employment who give a history of syphilis, or who show clinical signs of this disease, are rejected, and their eligibility is suspended until evidence has been submitted showing 2 years of adequate treatment.

Sailors and marines, like the civil-service employees, are given physical examinations prior to entry into the Navy or Marine Service, and only those free from venereal disease are accepted. A continuous effort is made to keep these people from becoming infected. Despite this effort men do become infected, and sometimes the rate of infections reaches alarming proportions. These infections are acquired from the civil population in the ports of call, and the venereal disease rate in the Navy is an index of the venereal disease conditions in the cities which are naval ports.

The strength of civil-service personnel in the navy yards is already greater than at any time during the World War, and the strength of the Navy and Marine Corps will soon exceed the average strength of 1917.

It is possible to predict with a great deal of accuracy how many cases of venereal disease will occur in the Navy and civil-service personnel unless a tremen-

dous effort is made in the civil communities to place the infected population under treatment and to keep them under treatment until they are no longer active. It is time to start a vigorous campaign of (a) law enforcement to suppress commercialized prostitution, (b) treatment of infected persons (enforced if necessary), and (c) a sensible plan for rehabilitation of the prostitute.

Parran's "Platform for Action" in his "Shadow on the Land" should be immediately implemented with men and money in order to conserve the health of the civil community and promote the efficiency of the Navy.

Venereal diseases are preventable. The cost of cure is greater than the cost of prevention.

Minnesota venereal disease control program in connection with military maneuvers. R. R. Sullivan. *J. Social Hyg.*, New York, 26: 371-376, Nov. 1940.

Beginning in April 1940 tentative plans were laid for a cooperative health program to meet problems expected to be created by the holding of military maneuvers in Minnesota in August, representing an influx into a tourist area of an estimated 40,000 troops. In July a meeting at the corps headquarters for the area was attended by nearly 100 percent of the health and law enforcement authorities of the entire maneuver area, in addition to representatives of the military, the United States Public Health Service, and State authorities. A program was worked out which included, among other points, provision for 4 under-cover agents to assist local authorities in the apprehension of prostitutes, provision for free diagnostic and treatment facilities and special laboratory services, and the survey of all resorts, cabin camps, etc., in and near the maneuver area.

A summary of these activities showed that a total of 32 persons were examined for venereal disease, and 6 new cases of gonorrhea and 6 of syphilis were treated in the area. Seven cases of gonorrhea were acquired in the maneuver area and

none of syphilis. Only 3 cases of gonorrhea and none of syphilis among the civilians were related in any way to soldiers. The 5 inspectors made 2,050 inspections of restaurants, hotels, cabin camps, and resorts; and no place was found where prostitutes were available. Five arrests of females suspected of being prostitutes were made the first week, but no further arrests were made. In all places of business the names of female employees were taken, and the operators were warned that the employment of girls who might be in the area for immoral purposes would not be tolerated.

Full tabulated data will be issued from the Seventh Corps surgeon's office at a later date.

Venereal disease in war-time. M. Officer, London, 64: 148, Nov. 2, 1940.

The provisions of Circular 2181 (Oct 23, 1940) issued by the Ministry of Health are considered. It has been decided by the Admiralty, War Office, and Air Ministry that economy of time, staff, and expenditure would be secured if out-patient continuation treatment and tests of cure on selected service cases could be conducted at civilian treatment centers after any initial treatment that it may have been considered necessary to administer in service hospitals. The Minister believes that the civilian treatment service should play the largest possible part in the treatment of members of the forces, and authorities of approved treatment centers are therefore requested to give every assistance to the service authorities by providing treatment. A letter is being sent to venereal disease officers setting out the methods of treatment suggested and of the recording of treatment and progress.

Provision is made for payment for treatment of venereal disease among service patients, and also for the costs of laboratory service.

In view of the new needs created by the war and of the calls on the treatment service likely to be made by members of the forces, the Minister has decided to assist the local authorities con

erned by the payment of a grant of 75 percent of approved expenditures incurred in extending the treatment service to meet war-time needs. These needs should be met in the main in rural areas by mobile units.

Parliament. Minister of Health takes stock. Venereal disease. *Lancet*, London, 2: 529, Oct. 26; 567, Nov. 2, 1940.

Malcolm MacDonald (Minister of Health) told the House of Commons on October 17 that the incidence of venereal disease in England had shown a large and steady decline over the last 20 years, but that there were indications during the last few months that it was once more on the increase. This was partly a result of the new large congregations of population which had been created around military camps and in the neighborhood of expanding war industries. In these places there was often no established service for the treatment of venereal diseases because there had previously been no great volume of cases to be dealt with. The service must now be extended, although the burden of financial responsibility should not fall mainly on the local authorities. MacDonald said that he had asked these local authorities to maintain or expand their treatment service or to create new units where necessary. He stated that there would be an Exchequer grant of 75 percent of the cost. Officers of the Ministry of Health were helping to establish an effective organization. In many rural areas a mobile unit would be the best means of achieving results.

The Minister of Health was asked whether the grant to local authorities of 75 percent of their war expenditure on venereal disease included expenditure on education and propaganda.

MacDonald replied that the grant is payable toward the capital and maintenance costs of new treatment facilities necessitated by wartime conditions. Questions of education are under consideration by the Ministry of Health, however.

Study of prevention of blindness from ophthalmia neonatorum. *Sight-Saving Rev.*, New York, 10: 211-233, Sept. 1940.

This report was prepared in cooperation with the National Society for the Prevention of Blindness through its consultative relationship with the Committee on Conservation of Vision of the State and Provincial Authorities of North America.

The committee requested that an individual record be supplied for each case of ophthalmia neonatorum reported to health officers during 1939. Such records are available for 37 percent of the total cases. Factors materially affecting the value of the study are the incompleteness of the information, on the individual record, the fact that 59 percent of the total records came from the State of Ohio, and the incompleteness in the reporting of cases to health authorities. As an illustration of the latter, during an investigation it was shown that whereas only 23 cases had previously been reported for the period to the Department of Health of New York City, this investigation turned up 1,344 cases of ophthalmia neonatorum among 192,478 births; among these were 141 gonorrheal cases, 11 of which ended in impaired vision.

The following facts are noted from the statistical tables which accompany this report for 1939. There were 2,305,634 live births reported in the States and Territories, with 2,960 cases of ophthalmia neonatorum, of which 370 were gonorrheal. The corresponding figures for the Provinces were 217,765 live births, 44 cases of ophthalmia neonatorum, with 6 gonorrheal cases. For the total cases of ophthalmia neonatorum AgNO₃ had been used as a prophylactic in 867 cases, with 12 cases resulting in impaired vision; other prophylaxis was used in 80 cases, with 1 case of impaired vision. There were 366 cases which were attended by a physician in a hospital and 606 in a home; 74 were attended by a midwife. For gonorrheal infections the interval between date of

birth and date when symptoms were first noted ranged from 1 day to 34, with a median of 5 days. Of these 341 cases, in 17.6 percent the interval was from 1 to 2 days; in 42.6 percent, from 3 to 6 days; and in 27.6 percent, from 7 to 13 days. The duration of medical care was from 1 to 118 days, with a median of 14 days; 30.6 percent of the cases were under treatment for from 7 to 13 days.

An inquiry into the working of the prenatal blood test law. Bull. Massachusetts Soc. Social Hyg., Boston, 10: 1-3, Nov.-Dec. 1940.

On November 1, 1939, the law went into effect in Massachusetts which requires every doctor caring for a pregnant woman to take a blood test for syphilis at her first visit, unless it had already been taken by another physician during the pregnancy. There is no provision in the law for the specific recording of the cases discovered by such tests, and since there are no penalties, the enforceability depends wholly upon the good faith of the medical profession. The law, however, does provide an instrument for increased educational effort, both among the medical profession and the general public.

After the law had been in effect 6 months, a questionnaire was sent to the

doctors in 4 communities or cities asking what they thought about the law and what they were finding. From the 6 questionnaires sent out, the replies of only 239 physicians had significant statistical value. On the replies of 239 doctors, 4,843 blood tests were reported and the 239 doctors reported only 17 cases (0.35 percent) with a positive blood test. This figure is in general within what might be expected according to other reports.

Seventy percent of the physicians replying believed that the law was effective. Five percent enumerated difficulties other than objections from their patients among which were the difficulties in getting the specimens to the State laboratory and in getting tubes from local board of health.

Of the 17 cases reported as positive, but 2 were tested before the fifth month of pregnancy. Eleven were given a diagnosis of syphilis, one congenital, and 6 of these had had no previous knowledge of the disease.

This law, if properly fortified by educational work, has the power of making the taking of blood from pregnant women for serologic examination as routine practice as is the dropping of silver nitrate into the eyes of the newborn.



Progress in the Control of Venereal Diseases in Virginia

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N VIRGINIA, the history of organized public health endeavor toward the control of venereal diseases is divided into two periods of activity. The first of these was initiated by the entrance of the United States into the World War. Attention became focused on venereal diseases at that time because of the high rate of infection discovered in men recruited for the military forces. Though designed to be intensive at its inauguration, this program was of relatively short duration, due undoubtedly to the fact that it was instigated by military authorities and because of the lack of public support and understanding of its objectives. The second era of venereal disease control activity began in 1936. Fortunately, this period was not associated with a war-time emergency. It began under more normal circumstances as the result of Nation-wide education and publicity sponsored by public health authorities, public educators, and the medical profession. The past 4 years have seen the conservative, though consistent, growth of this activity to its present position, a definitely coordinated part of the general public health program in Virginia.

The first program developed for the control of venereal diseases in Virginia was begun in 1918. During April of that year a meeting of representative officers of the United States Public Health Service, the Commission on War Training

Camp Activities, and the Virginia Department of Health was called to discuss measures that would influence the control of these diseases.

In July 1918 the Interdepartmental Social Hygiene Board was created by an act of Congress. Among the duties of this Board was the responsibility of devising and recommending a broad program for the control of venereal diseases throughout the United States and the coordination of the control measures developed by State boards of health and the United States Public Health Service.

The complete program recommended by the Interdepartmental Social Hygiene Board was adopted in Virginia. Active prosecution of the program began in January 1919, at which time a full-time director was appointed to head the newly created division of venereal diseases in the State department of health. In addition to the administration, the program was concerned with three principal activities (1) (1) Repressive measures, (2) treatment, and (3) education and publicity.

Several laws were enacted as the result of the interest and importance attached to the venereal diseases by the public and legislative bodies at that time. These laws (2) provided for the examination and punishment of persons convicted of prostitution or keeping houses of ill fame and for commitment of such persons to city farms or hospitals; prohibited advertising concerning venereal diseases; prohibited soliciting, aiding, or permit-

¹Detailed to Virginia Department of Health.

ting prostitution or illicit sexual intercourse; prohibited marriage of persons with contagious venereal disease. The prohibition of marriage is described in the law as follows: "That no woman under the age of 45 years, or any man of any age, except he marry a woman over the age of 45 years, either of whom is a habitual criminal, idiot, imbecile, hereditary epileptic, or insane person, or *any person of any age, who is afflicted at the time with any contagious venereal disease*, shall hereafter intermarry or marry any other person within this State."

This law did not require a serologic test for syphilis or physical examination unless the clerk on his own initiative requested evidence of freedom from disease. It will be interesting to note the decided change of thought when this act is compared with recent legislation concerning marriages, passed by the General Assembly 1940, presently discussed in this paper.

The State board of health in June 1918 adopted additional rules and regulations for the control of venereal diseases. Syphilis, gonorrhea, and chancroid were declared dangerous, infectious, and communicable diseases. The most important of these rules (3) provided (a) for the reporting of venereal diseases to the local or State department of health; (b) for mandatory instruction of infected persons by physicians regarding measures to follow in preventing the further spread of their diseases; (c) for the examination of individuals reasonably suspected of having a venereal disease and quarantine of infected persons dangerous to the public health. The term "reasonably suspected" was interpreted in the regulations as applying to vagrants, prostitutes, keepers, inmates, employees, and frequenters of houses of ill fame. It is apparent from this application that a conviction had first to be obtained on one of the above designations before an examination could be accomplished on a suspect (contact) who was unwilling to submit voluntarily. The regulations

(still operative) do provide, however, for the quarantine of known infectious or potentially infectious persons who are conducting themselves in such a manner as to be a public health menace. This provision enables the health officer to isolate such cases and is employed at the present time when recalcitrant persons become delinquent in their treatment. As a rule, such a person would rather resume treatment than be quarantined for an extended period of time to his home, jail, State farm, or such place as the health officer might designate. These rules and regulations were enacted into law by the General Assembly in extra session August 1919.

The staff of the division of venereal diseases was particularly active in prosecuting the repressive measures of the program. Reports and assistance were rendered local police authorities in suppressing violations of laws against commercial vice, detailed investigations were made of hotels and rooming houses, and arrests were made on charges of soliciting or procuring for immoral purposes. Chauffeurs were successfully prosecuted for using automobiles in transporting persons for acts of prostitution, and a number of persons were convicted of keeping houses of prostitution.

Treatment of the venereal diseases was provided at the two existing clinics at the University of Virginia Hospital and the Medical College of Virginia, and at the new clinics organized in the larger cities of the State during 1918 and 1919. The salary of a clinician was provided for the operation of these treatment dispensaries, and arsphenamine and mercury preparations were furnished without charge. These drugs were also furnished to penal and charitable institutions and to the industrial schools for white and colored girls.

On April 1, 1918, the State department of health laboratory began performing the Wassermann test, and in 1919 inaugurated the service of examining smears for the identification of the gono-

occus. These examinations were made without charge.

The education and publicity features of the control program were energetically applied and accomplished principally by means of public addresses, lantern slide demonstrations, motion picture films ("Fit to Win," "The End Of The Road," etc.) and by the distribution of bulletins and pamphlets. Particular emphasis was placed on social hygiene and the morbid degenerative changes resulting from infection with a venereal disease.

The control program as it had been organized was making satisfactory progress until July 1920, at which time Federal appropriations were curtailed. The original Federal appropriation of \$22,155.58 allotted by the Interdepartmental Social Hygiene Board, together with 11,000 contributed by State agencies, provided a budget of \$35,415.58 for the year 1919. Federal funds to Virginia were reduced in 1920 to \$12,246.65. A small reduction was made each year until by 1925 the allotment was only \$546.11. There was no Federal appropriation in 1926. State appropriations reached a low of \$2,200 in 1924 and in 1926 increased to 7,000. However, the amount of money available after July 1, 1920 was insufficient to conduct a satisfactory program and each succeeding year witnessed a rapid disintegration of the control program.

In the fall of 1920 the full-time director of the division of venereal diseases resigned. The name of the division was changed to the "bureau of social hygiene." Financial assistance to all but free of the venereal disease clinics was discontinued and the distribution of antisyphilitic drugs restricted to the 12 operating clinics. In 1925 all financial assistance as well as free antisyphilitic drugs and the vestiges of other services, except the educational program, were discontinued. Educational work was continued under the direction of a woman educational director who confined her activities essentially to addressing

lay organizations, college and school groups of women and young girls. Social hygiene was the general theme. This portion of the remaining program was also discontinued in 1930. A few of the clinics in the larger cities continued to function under the direction of local health departments, with funds provided by local governmental bodies. The collection of morbidity and clinic activity reports was transferred to the bureau of communicable diseases. The only activity henceforth that might be construed to have any relationship to a venereal disease program, except the performance of serologic tests for syphilis and examination of smears for the gonococcus, was an agreement with the Virginia Social Hygiene Council (a branch of the Medical Society of Virginia) to purchase at wholesale rates and to distribute at cost to physicians certain drugs used in the treatment of syphilis.

Through the cooperative efforts of the Julius Rosenwald Fund, the United States Public Health Service, and the Virginia Department of Health a local demonstration in the control of venereal diseases was organized for one city and the surrounding county (4). This demonstration began in January 1931 and continued over a period of 16 months. During this period 3,812 Negroes were given serologic examinations, and of this number 339 (8.9 percent) were found to have positive serologic reactions. During 1934 a serologic resurvey was made of this same county and city, and of 1,949 persons examined, 358 (13.3 percent) had positive tests. Serologic surveys were also conducted by the State department of health in several other counties and cities in the State. A total of 2,976 colored and 403 white persons were examined, of which 11.1 percent and 4.4 percent, respectively, had positive serologic reactions.

Although there was no organized program from 1930 to 1936, considerable effort was devoted to fact-finding activities and this served subsequently to create new interest in the problem.

With the stimulus of Nation-wide publicity focused on syphilis and gonorrhea in 1936 and the recognition of these diseases as a major health problem, interest was revived in Virginia in the organization of a program of control. On December 4, 1936 an officer of the United States Public Health Service was detailed to the Virginia Department of Health for the purpose of cooperating in the development of a plan for the control of the venereal diseases. Shortly thereafter a division of venereal disease control was created in the bureau of communicable diseases, functioning as an autonomous division. On February 1, 1937, a director for this division was appointed as a full-time officer by the State Health Commissioner.

In that same year the Medical Society of Virginia appointed a committee to review the available information on the problem of syphilis control in Virginia and to make recommendations. A quotation from the report made by this committee serves to express its opinion; "The present program is entirely inadequate. The necessary changes and additions will require substantial financial appropriations. The responsibility of eventually eradicating syphilis must be accepted by the general medical profession. We hope that the organized public health facilities will be able to secure appropriations which will allow them to take a more active leadership in the program."

During the fiscal years 1937 and 1938, \$12,000 and \$30,000, respectively, were allotted for the control of venereal diseases from funds provided by the Social Security Act. In subsequent years both State and Federal funds have been appropriated to carry on the program. The General Assembly of Virginia in 1938 appropriated \$23,830, viz, \$11,915 for each year of the biennium. This sum of money, together with an allotment of \$58,983 from the United States Public Health Service, provided a budget of \$70,898 for the fiscal year 1939. For the present year, ending June 30, 1940, the budget totals \$118,312, of which the State contributes

\$11,915 and the United States Public Health Service \$106,397. The General Assembly in 1940 appropriated \$54,000 for the control of venereal diseases in Virginia during the next biennium.²

The first step undertaken in the organization period of the present venereal disease control program was a study of all available material bearing on the incidence and prevalence of the venereal diseases in Virginia. It was realized that such a definition would vary in the several sections of the State because of the variation in the social, economic, and racial distribution of the population. The rate of infection in the colored race is considerably higher than that of the white race and is undoubtedly due to the fact that more Negroes in comparison to the white population fall into the lower economic and social brackets.

The July 1930 census records the total population of Virginia as 2,425,000—white, 1,774,000 and colored, 651,000. Approximately 26 percent of Virginia population, therefore, is colored, and the distribution of this race in the State is important from the standpoint of the prosecution of more intensive control activities in the several sections where the colored population is relatively greater.

The percentage of the State colored population is greater in the southeastern section of Virginia. Each of seven counties contain over 2 percent of the State colored population. Further, the problem of any community depends upon the percentage of the colored population of the individual county. In each of six counties the proportion of colored to total population is 60 percent or over.

Inasmuch as morbidity case reporting for syphilis and gonorrhea in Virginia has been far from complete, an attempt to estimate the incidence of these diseases was based on serologic surveys of the general population conducted during the past several years. Applying the

² Local appropriations for the control of venereal diseases not included.

percentages (white, 4 to 5 percent; colored, 15 percent) to the State population, it has been estimated that there are 180,000 cases of syphilis, of which approximately 90,000 cases exist in the white population and a similar number in the colored.

Data obtained from the five State hospitals for mental diseases in Virginia showed that 264 cases of syphilis were admitted in 1937. This averaged 7.9 percent of all admissions to these institutions. It cost the State \$112,233.62 to maintain this group of syphilitic patients for the year.

A new program for the control of venereal diseases in Virginia was formulated in 1937. It embraces the principal features of the advisory committee's report to the United States Public Health Service, setting forth "Recommendations for a Venereal Disease Control Program in State and Local Health Departments (5)." At the October 1937 meeting of the Virginia State Medical Society a resolution was adopted by its members endorsing the plan for the control of venereal diseases as had been formulated by the Virginia Department of Health.

The Virginia program includes the following:

1. Morbidity reporting.
2. Treatment facilities.
 - a. Clinics.
 - b. Free distribution of antisyphilitic drugs.
 - c. Standardization of treatment.
 - d. Special diagnostic centers.
3. Laboratory facilities.
4. Epidemiologic service.
5. Professional informative program.
6. Lay education.
7. Prophylaxis.

Venereal diseases were made reportable to the State department of health in Virginia by the enactment of a law on March 20, 1920. Morbidity reports were originally received at irregular intervals at such times as cases occurred in the practice of physicians. In 1932 a weekly morbidity report card including all reportable communicable diseases was

adopted by the department. Since a satisfactory classification of the venereal diseases was not possible under this system, a separate means of reporting syphilis and gonorrhea was inaugurated January 1, 1938.

In counties and cities with full-time health departments, in which jurisdictions the case reports are made directly to the local health agencies which in turn transmit them to the State department of health, a case report form which provides for contact information has been developed. The case report identifies the patient by means of serial number and/or patient's name or initials (optional). The classification of disease is the same as that recommended by the United States Public Health Service (6). Notification of delinquent patients is provided for by the use of a second card which remains attached to the physician's record book, but which can be removed and forwarded to the local health department for action when individuals fail to return for necessary treatment. The remaining stub in the record book is designed to serve as a permanent record of treatments if the physician so desires. These three forms are provided on a single 9" x 5" card perforated into the three sections: (1) Case report and contact information; (2) delinquent notice; (3) physician's treatment record. Ten such complete forms are bound in heavy Manila paper and arranged in a booklet.

In cities and counties without full-time local health service, in which areas physicians report directly to the State department of health, a case report card with identical classification of diseases but without provision for contact information has been adopted. The form used in these sections does not contain the delinquent notice card.

The use of these report forms was begun in 1938, during which year the number of cases of syphilis reported to the department more than doubled the previous year's figures. It is believed that the new system of reporting was responsible in some measure for this improvement,

though the distribution of free drugs contingent upon case reports perhaps had more influence. Figure 1 shows the number of cases of syphilis and gonorrhea reported yearly in Virginia from 1919 through 1939. Of material value, however, has been the opportunity for a more detailed analysis of venereal disease case data afforded by the present record forms. In addition, the provision of contact information and delinquent treatment notice in areas served by local departments, though not thus far utilized to a satisfactory degree, should, as the local programs develop, serve an important need. Approximately 10 percent of case reports have contained contact information. During the same period, 1,204 notices of discontinuance of treatment have been received.

In December 1936 there were 19 venereal disease clinics throughout the State. This number has been increased to 108 as of January 1, 1941. A total of 148 clinic sessions are now being held each week. Approximately 45 of the 108 clinics are located in the southeastern sections of the State, where the largest Negro population is. The State department of health assists in the operation of these

clinics by furnishing all necessary record forms, free antisyphilitic drugs, and certain equipment. Payment of an honorarium to private physicians conducting the clinic sessions, and consultation service by staff members of the division of venereal disease control are also provided by the department.

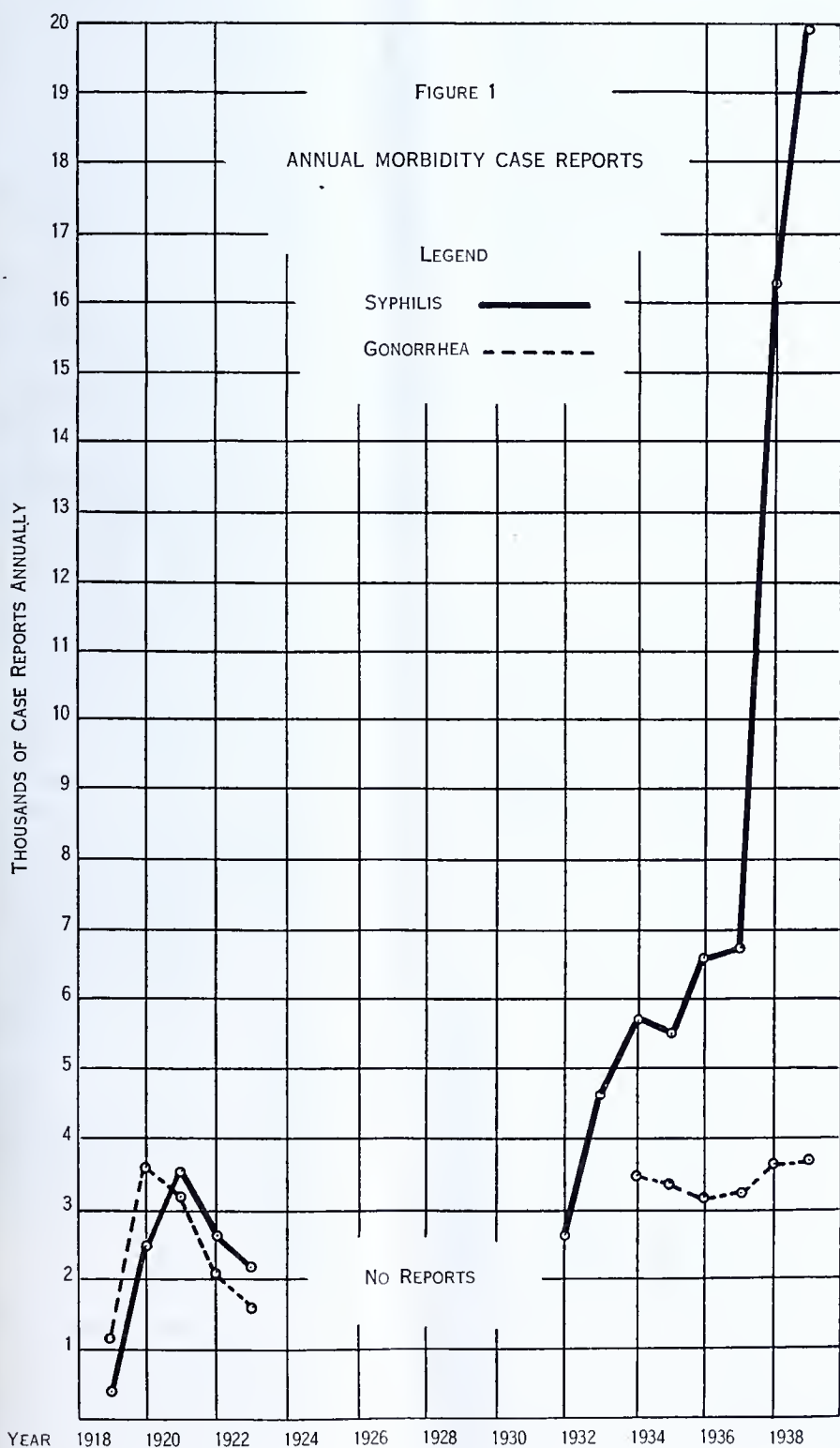
The majority of clinics are located in cities and counties having full-time health service. In such instances the health officer is responsible for the administration; the public health nurse arranges the clinic setup and assists in its operation; local practicing physicians, recommended by their medical society, perform the clinical examinations and administer the treatments. The practitioners serve on a rotating schedule of not less than 3 months each. Recommendations regarding the diagnosis and standardization of treatment for syphilis have been introduced in all clinics. Either the health officer or the nurse obtains the contact histories from patients and conducts the case-finding and case-holding activities. Table 1 shows a summary of the activities of the clinics cooperating with the Virginia Department of Health during the fiscal years 1938 and 1939.

TABLE 1.—Clinic activities

Fiscal year	New cases admitted		Number of treatments administered			Number of visits for treatment, examination, or advice	Social service visits	
	Syphilis	Gonorrhea	Arsphenamine	Bismuth	Gonorrhea		Contacts	Delinquents
1937-38.....	4,648	530	58,128	42,552	3,270	121,687	7,110	20,231
1938-39.....	9,658	1,146	139,420	130,271	7,079	317,876	8,598	47,989

On October 10, 1938 the service of distributing free antisyphilitic drugs to physicians, hospitals, and clinics (excepting State and Federal institutions) was inaugurated. These drugs are furnished for all cases of syphilis, regardless of the patient's economic status, and are distributed on the basis of case reporting. Hospital and clinic requisitions for drugs are not limited to any specific quantity.

A physician's requisition for a single case, however, is limited to 10 ampules of an arsenical, 10 ampules of distilled water, and one 30-cc. bottle of bismuth. A physician is permitted to submit as many requisitions at any one time as he has cases of syphilis in his practice. He is also allowed to reorder for the same case after an interval of 8 weeks from the date of the last requisition.



The following drugs are distributed:

Arsphenamine.....gm..	0.4	3.0		
Nearsphenamine.gm..	.3	.45	0.6	3.0
Sulfarsphenamine.gm..	.2	.3	.4	
Mapharsen.....gm..	.04	.06	.6	
Triple-distilled water.....cc..	10	50		
Bismuth subsalicylate in oil (bottles)	30	100		

These drugs are furnished to 9 city and 29 county health departments for distribution in their respective jurisdictions.

In counties without full-time health service, these drugs are furnished directly from the State department of health.

Table 2 shows the number of individual physicians, hospitals and clinics receiving drugs over two comparable nine-month periods, the quantity of drugs supplied, the estimated number of doses, and the cost price of the material distributed.

TABLE 2.—Distribution of antisyphilitic drugs

Period	Physicians	Clinics and hospitals	All arsenicals			Bismuth			Distilled water		Total value
			Grams	Doses	Value	Cubic centimeters	Doses	Value	Cubic centimeters	Value	
Oct. 10, 1938 to June 30, 1939...	979	104	62, 992.4	224, 130	\$28, 369.60	261, 840	130, 910	\$2, 417.32	1, 270, 200	\$4, 833.60	\$35, 620.52
July 1, 1939, to Mar. 31, 1940...	886	117	61, 245.0	226, 490	27, 267.14	297, 045	274, 762	1, 685.76	1, 373, 850	4, 571.64	34, 708.22

Figure 2 presents graphically the estimated number of doses based on the quantity of drugs supplied to private practitioners and to clinics and hospitals during these two 9-month periods. It is interesting to note that private physicians have been about equally divided in their choice between nearsphenamine and mapharsen, whereas hospitals and clinics decidedly have used much more mapharsen. Arsphenamine is now being requested by relatively few private physicians and in only two clinics in the State.

Satisfactory laboratory facilities are of basic importance in any venereal disease program. Fortunately, in Virginia the serologic test for syphilis and the examination of smears for the identification of the gonococcus, added as regular services in 1918 and 1919, respectively, have been available continuously without charge to the profession. In April 1937 the delayed dark-field examination was added as an additional service in the central laboratory at Richmond, and was provided in the three district laboratories located at Abingdon, Luray, and Norton in 1938.

Beginning in 1932 periodic attempts were made to check the efficiency of the

examinations performed in the State department's laboratory through the co-operation of public health and institutional laboratories in this and other States. Because of the considerable variability in regard both to the type of tests and techniques followed in the participating laboratories no truly reliable comparison of results was possible. Thus the inauguration in 1937 of the evaluation studies conducted by the United States Public Health Service for State laboratories afforded a more dependable method of analysis. The two tests performed in the central laboratory of the department (Kahn standard flocculation and a complement fixation method) have had satisfactory specificity and sensitivity ratings in each of the annually conducted evaluation studies with the exception of the sensitivity of the complement fixation reaction during 1939, which was promptly remedied.

In March 1940 an invitation was extended to the 66 other laboratories in Virginia performing serodiagnostics for syphilis to participate in a similar evaluation study. Thirty accepted the invitation. This study is now in progress.

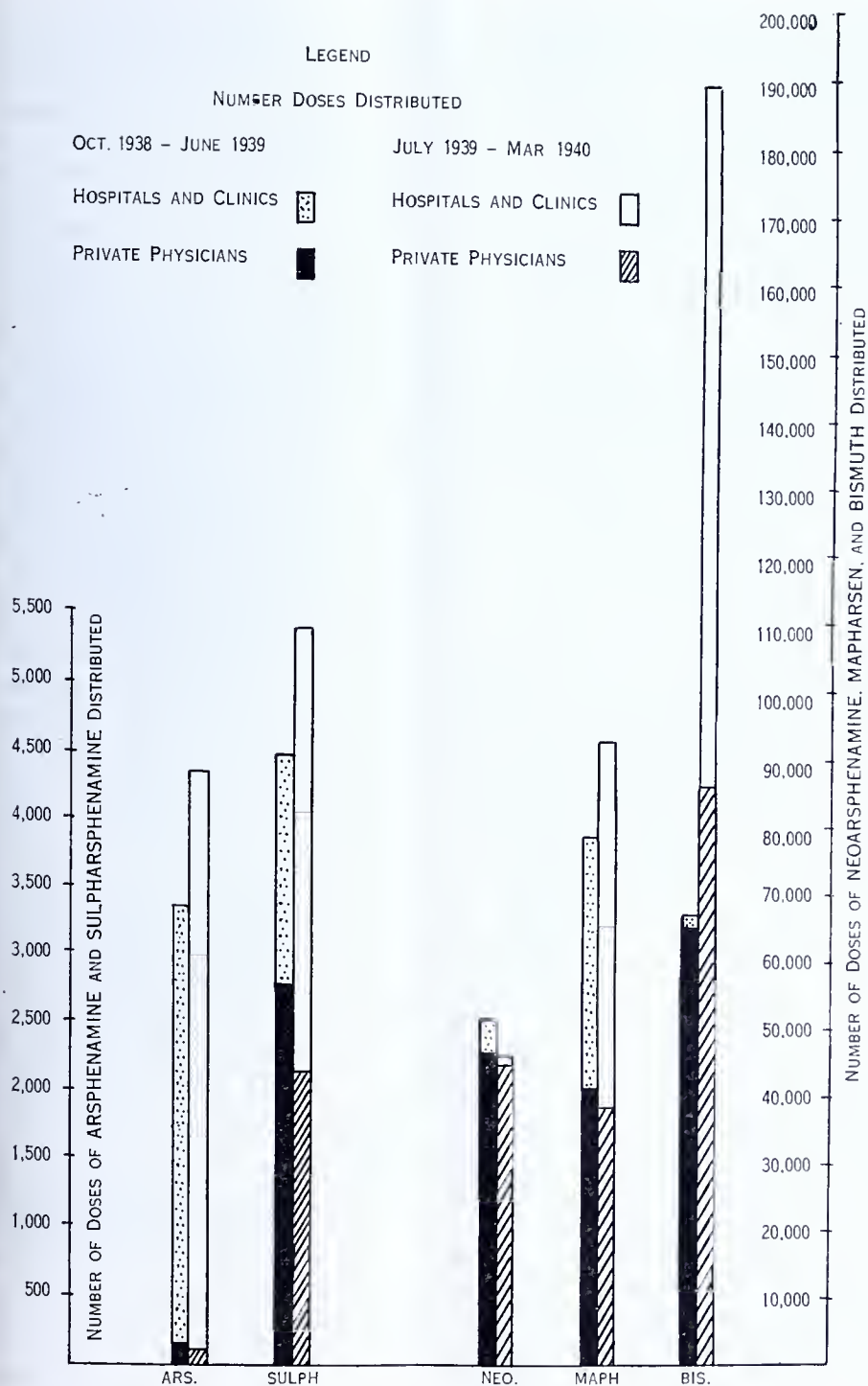


FIGURE 2. Distribution of antisyphilitic drugs to private physicians, hospitals, and clinics.

The use of serodiagnostic tests for syphilis has consistently increased from year to year with few exceptions from its date of adoption by the health department.

With the inauguration of the present program in 1936, however, the demands for this service increased to such a degree, and has continued to increase since that

time, that it has been necessary to employ three additional serologists in the Richmond laboratory. At the present time approximately 50 percent of the total number of all laboratory examinations are for the diagnosis of syphilis and gonorrhea. Figure 3 shows the annual number of serologic examinations for syphilis performed in the health department's laboratory during the period 1918-1939.

The development of an epidemiologic program was begun in January 1938 at the time the revised system of case reporting was inaugurated. It is apparent from the previous description of provisions made for contact follow-up in the reporting system that an effort has been made to encourage physicians to utilize an epidemiologic service.

In an effort to develop an efficient program of this nature in the various local departments, group meetings, conferences, and informal discussions have been held in several sections of the State for the purpose of informing health officers and public health nurses of the proper methods and procedures consistent with current opinion and practice in this field. On July 1, 1939, a public health nurse who had previously received training in applied epidemiology was appointed to the staff of the division of venereal disease control to serve in the capacity of a consulting field nurse. Her services are being directed toward the instruction of, and consultation with, local public health personnel concerning the selection and handling of clinic patients, routine handling of records, selection, maintenance and use of clinic equipment, and the technique of case-finding and case-holding. The bureau of public health nursing cooperates in carrying out these procedures.

The development of an informative program for physicians, health officers, and nurses has occupied an important position in the Virginia program. Particular emphasis has been placed upon the clinical manifestations, diagnostic procedures, and methods of treatment. The public health aspects of the program have been

stressed in detail to public health workers, and the objectives have in addition been presented to private practitioners. The staff of the division of venereal disease control has participated in medical society meetings, conferences of health officers and nurses, and other professional gatherings. Papers have been presented on different aspects of the problem, motion pictures shown, and informal discussions held. A variety of literature dealing with the clinical and public health aspects of the venereal diseases has been sent from time to time to physicians and public health workers throughout the State (7). The results of this phase of the general program have been encouraging and are evidenced by the noticeable improvement in the standards of diagnosis and treatment adopted both by the clinics and individual physicians participating in venereal disease activities.

Nation-wide publicity on the subject of venereal diseases was influential in preparing the attitude of the public mind in Virginia in regard to an intelligent consideration of these diseases. With this preparation, lay opinion was in accord with the purpose and objectives of the organized control program. Venereal disease information has been presented by means of public addresses, motion pictures, and demonstrations before civic organizations, high schools, colleges, and many other professional and lay groups. In addition, the radio, newspapers, departmental publications, bulletins and folders have been utilized to a considerable degree.

At the meeting of the general assembly in 1940 a bill requiring additional regulations for the issuance of marriage licenses was passed and became effective August 1, 1940. The intent of this bill is the same as that of other States which have in the past few years enacted similar marital legislation. The Virginia marital law, however, differs from similar legislation recently passed in other States in that the marriage of persons with syphilis is not prevented. The law provides that all persons desiring a license

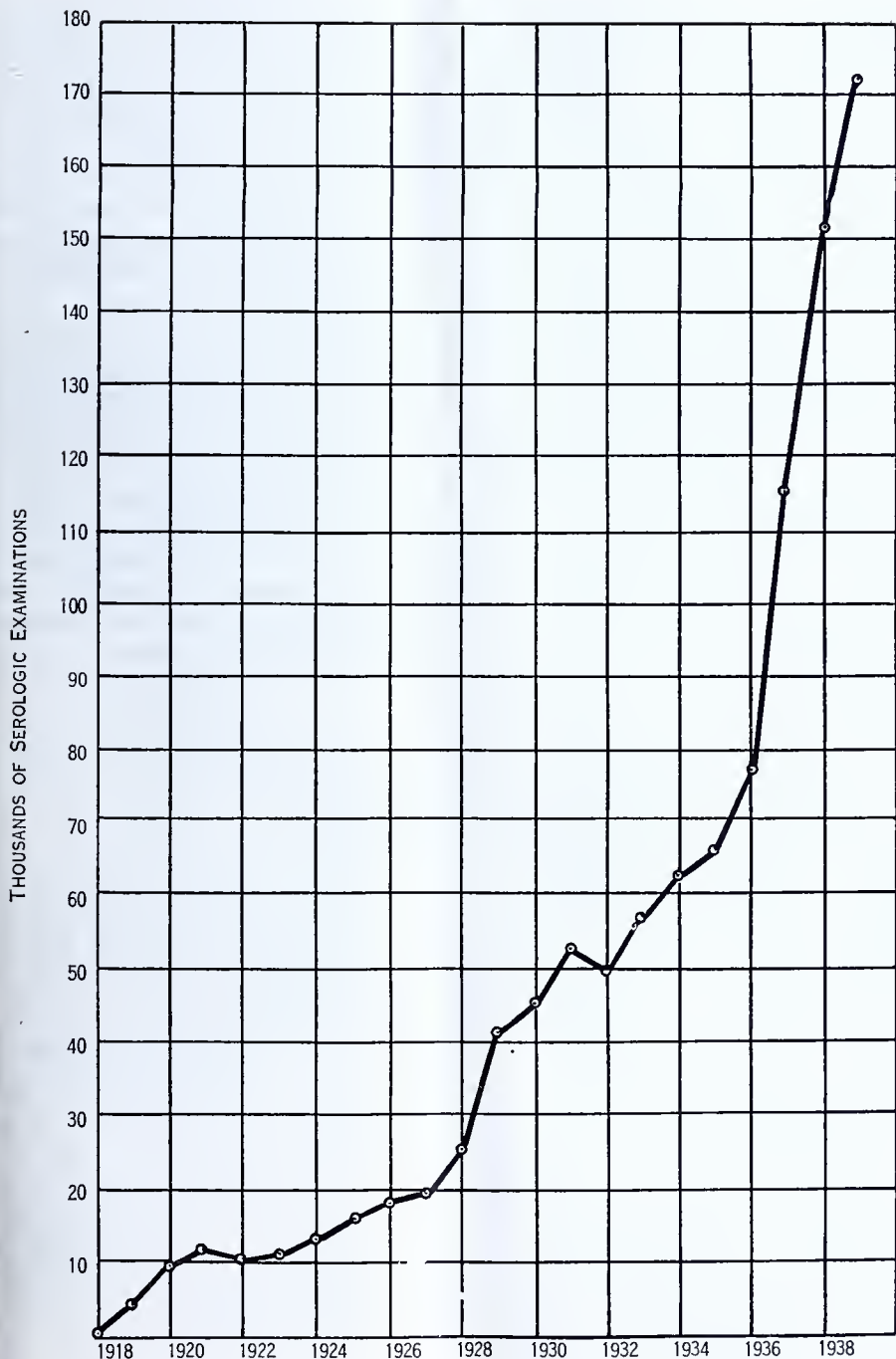


FIGURE 3. Annual number of serologic examinations for syphilis performed by Virginia Department of Health.

onarry must have a serologic test for syphilis.

he physician is directed to forward specimens of blood for serologic examination only to laboratories approved for

such purpose by the State health commissioner. Serologic evaluation studies of laboratories provide the basis for such approval. Upon receipt of a laboratory report which does not indicate evidence

of syphilis the physician may issue a certificate for the person desiring to secure a marriage license. Should the laboratory report reveal evidence of syphilis, the physician will then repeat the test, obtain a history, and make a physical examination. If a diagnosis of syphilis is established, the physician, in person, must inform both the person examined and the other person for whom the marriage license is desired of the result of the serologic test, the nature of the disease, and the possibilities of transmitting the disease to the marital partner and to their children. After such a conference the physician is authorized to issue a certificate which will enable the person to secure a marriage license. No information is given the clerk of the court other than the fact that the law has been complied with.

Should one or both persons desiring to marry have syphilis, and having complied with the above regulations proceed with the marriage, the language of the law states that it is deemed that they have agreed to take treatment and such precautions to prevent the spread of infection as may be prescribed by the State health commissioner. Failure or refusal to take or continue treatment or precautions prescribed will cause such a person to be guilty of a misdemeanor and upon conviction to be punished accordingly.

The development of an effective program of prophylaxis in civil populations has been and continues to be a difficult problem to solve. Though admitted that mechanical and chemical prophylaxis are attended with at least some degree of success when properly employed, the administration of such procedures has found efficient application only in military or similar regimented organizations. In addition, certain important aspects of this particular problem cannot be as easily divorced either actually or in the minds of the general public from sex and morals as have other portions of the program for the control of venereal diseases. It is believed, therefore, that since

we have but recently been able public to establish syphilis and gonorrhea communicable diseases and to present them as medical problems, it would be wise to delay the adoption of any generalized effort of this nature until a more practical application of these measures can be evaluated, or certainly until the danger of jeopardizing the progress made thus far can be eliminated.

The Virginia venereal disease control program as it has been developed to the present time includes the basic principles recommended by authoritative sources. It is believed that, with continued and adequate financial support through State and Federal appropriations, together with the cooperation of the medical profession and an enlightened, intelligent public, that this program now in its infancy will continue to show progress.

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Extragenital Chancroid

A Case Report

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EXTRAGENITAL chancroid infection is quite rare (1, 2) and therefore liable to be misdiagnosed. If, however, the possibility of such an infection is kept in mind, it is not difficult to substantiate the suspicion in an individual case by the use of appropriate methods.

The following presentation is illustrative:

E. C., white soldier, 28 years of age, was admitted to the hospital October 30, 1939. He stated that his right middle finger had been scratched with a brass instrument on October 3. On the same night he and a friend had been "playing" with a girl. (The friend was said to have had a penile lesion but no sore on the finger.) The scratch did not bother him until the next morning, at which time pain and swelling set in. Bathing in a solution of Epsom salt afforded some relief. On admission the patient had an ulcer $1\frac{1}{2}$ inches in diameter on the right middle finger extending proximally from the matrix of the nail. The ulcer was sharply defined, with a somewhat undermined margin, and was slightly indurated but not inflamed. The swollen epitrochlear glands were visible, and were matted together to some degree. The overlying skin was intensely red. Suppuration was beginning. The patient had no fever.

Inspection of the genitalia revealed an indurated ridge in the middle of the dorsum of the glans penis. According to the patient it had appeared 5 days earlier (October 25) and had been suppurating

but was not tender. Inguinal glands were not palpable. The haemogram showed W. B. C., 14,590—polymorphonuclears, 79 percent; lymphocytes, 17 percent; monocytes, 4 percent.

With respect to the afebrile condition in a suppurative lymphadenitis, the assumption of a simple pyogenic cellulitis seemed unlikely.

Routine bacteriologic cultures from the ulcer made on October 31 were reported essentially negative. Smears stained by Gram and Ziehl-Neelson methods were also negative. Staphylococci were recovered from the penile ulcer. Repeated examinations for spirochetes in material obtained from the finger and penile lesions were negative.

November 2. Considerable fluctuation had developed in both glands of the epitrochlear bubo. Aspiration of the lower gland yielded 4 cc. of yellow pus and was followed by collapse of both glands. Routine cultures from this material were negative.

November 4. Chancroid and Frei intradermal tests were done.

November 5. The agglutination test for tularcemia was negative.

November 6. The intradermal test for chancroid was strongly positive, the Frei test negative.

November 10. On the strength of the positive skin test for chancroid, the bubo was aspirated again and the pus subjected to special culture technic for the isolation of Ducrey's bacillus (3, 4, 5). The organism was recovered.

It is known that extragenital chancroid, rare as it is, occurs more frequently as a subinfection from a genital lesion than as a primary infection (1, 2). This patient stated clearly that the penile lesion was much more recent than that on the finger, and the findings were in accord

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This study was aided by a grant from the U. S. Public Health Service to the University of Georgia School of Medicine for research studies in the diagnosis and treatment of chancroid, granuloma inguinale, and venereal lymphogranuloma.

with this statement. As to diagnosis, however, the question whether this was a true primary extragenital chancroid is irrelevant. The patient did not come to the hospital for the penile lesion and failed even to comment on it. In localized minor surgical cases a complete examination of the body will hardly be the rule unless the patient is admitted to the hospital. Under these circumstances the diagnosis must be made from the lesion presented and the concomitant symptoms. In the case reported, suspicion was aroused by the character of the ulcer, poor healing tendency, development of bubo, and negative routine laboratory examinations (cultures and smears). The suspicion was supported by the positive skin test for chancroid and confirmed by positive culture when an appropriate method was utilized. These tests are being more fully recognized as valuable adjuncts in the recognition of chancroidal infection. It should be emphasized that, as with the Frei test, a positive skin test for chancroid can mean a *past* as well as a *present* infection. The diagnosis of an existing lesion therefore must rest on the interpretation of clinical findings and laboratory tests taken together.

Summary.—A case of primary extragenital chancroid with secondary penile lesion is reported. The incident stresses the value of the intradermal test for chancroid, and the use of appropriate laboratory technic in the cultivation of Ducrey's bacillus.

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DIAGNOSIS

A survey of sixty-eight cases of extragenital chancres. U. J. Wile and Herbert H. Holman. *Am. J. Syph., Gono. & Ven. Dis.*, St. Louis, **25**: 53-66, Jan. 1941.

The material for this report was gathered from the records of the department of dermatology and syphilology in the University of Michigan Hospital over a period of approximately 25 years (1914 through 1939.) The total number of cases of primary syphilis was 841. Of these, 68 (8 percent) had extragenital chancres. The number of these chancres in males was 43 (63.2 percent of the 68)—24 (35.3 percent of the 68) on the lip, 8 on the tonsil, 4 on a digit, 1 on the tongue, 2 on the pharynx, 1 on the palm, 1 on the forearm, 1 on the chin, and 1 on the anus. The number of these chancres in females was 25 (36.8 percent of the 68)—15 (22 percent of the 68) on the lip, 2 on the tonsil, 2 on a digit, 4 on the tongue, and 2 on the breast.

The lip was thus by far the most frequent site. Chancres of the lip were initiated most frequently in the act of osculation. A less common mode of transmission of the spirochete was found in sexual perversion, such as cunnilingus and fellatio. Mediate infection may also occur through contact with an inanimate object which harbors virulent spirochetes.

The authors discuss 22 of the cases briefly. Four of the patients were physicians who had been infected by patients. Three of these physicians had digital chancres, the fourth had primary syphilis of the palm.

Early syphilitic hepatitis with jaundice.
Report of a case. Herbert Rattner
and R. M. Reifler. *Am. J. Syph.,*
Gonor. & Ven. Dis., St. Louis, 25:
56-57, Jan. 1941.

Hepatitis with jaundice in early untreated syphilis is said to occur about once in 1,000 cases. The authors report the case of such a patient with untreated syphilis and acute hepatitis and jaundice. He was apparently successfully treated with an arsenical preparation.

The symptoms which caused him to seek treatment were malaise, loss of appetite, increasing yellowness of the skin, and a temperature of 100.4° F. The liver edge was palpable 6 cm. below the right costal arch and was tender to palpation. There was a generalized maculopapular eruption. The stools were clay colored. The icteric index was 107; cholesterol, 180 mg. per 100 cc. of blood serum; cholesterol esters, 20 mg. per 100 cc. of blood serum. The blood Wassermann reaction was strongly positive. The eruption was that of secondary syphilis, a generalized maculopapular eruption, with discrete lesions disposed symmetrically. The palms and soles contained papules with collarette scales. Moist papules were present under the foreskin, on the scrotum, and about the anus. Serum from these papules contained *Spirochaeta pallida*. On the glans penis there was a large lesion, almost healed, which apparently had been the chancre.

A diet rich in carbohydrates and capsules of bile salts were given. After the first injection of 0.15 gm. of neoarsphenamine, the feces and urine began to lose their abnormal colors, the pruritus was less intense, and there was a diminution of the tenderness over the liver edge. Within 10 days the patient received four injections of neoarsphenamine. At this time, the urine and feces had become a normal color, the urine was free from bile and urobilinogen, the icteric index was reduced to 34, the blood count was normal, there was no longer any pruritus, and the papular eruption had faded com-

pletely. The liver edge could not be palpated, and the tenderness over this area had disappeared. The blood Wassermann reaction was still strongly positive; the blood cholesterol, 193 mg. per 100 cc. of serum; and cholesterol esters, 92 mg. per 100 cc. of serum.

On the specificity of serologic tests for syphilis as determined by 40,545 tests in a college-student population.
Harry Eagle. *Am. J. Syph., Gonor. & Ven. Dis., St. Louis, 25: 7-15, Jan. 1941.*

Serologic tests for syphilis were carried out in 25 universities on a total of 40,545 white students of both sexes. Sixty-two (0.15 percent) had positive or doubtful tests confirmed by repeat specimens. Twenty-one of these presented clinical evidence or gave a definite history of syphilitic infection, and five others had previously received antisypilitic treatment, with no available data as to why that treatment was instituted.

Thirty-six students (an incidence of 1 in 1,125 tested) had repeated positive or doubtful serologic tests in the absence of clinical evidence or history of syphilitic infection, and might therefore possibly be nonsyphilitic persons giving biologic false positive serum tests for syphilis. However, the correlation between the incidence of clinically proved syphilis and these supposedly false reactions in the individual schools was so high (ungrouped coefficient of correlation 0.83) as to suggest that approximately 26 (70 percent) of these clinically unconfirmed tests actually represented latent syphilis.

The author believes it to be an open question whether the remaining 10 cases (an incidence of 1 in 4,000 tested) represented latent syphilis, false positive reactions due to an unrecognized intercurrent infection, or biologic false positive tests for syphilis occurring in normal individuals. The incidence of such reactions in the population tested seemed sufficiently small to justify, as a general public health measure, the diagnosis of syphilis in clinically normal individuals on the basis of

repeatedly positive serologic tests, even in the absence of history or clinical evidence of syphilitic infection. In individual cases, however, and particularly in population groups in whom the incidence of syphilis is known to be small, attempts should be made to differentiate between a possible biologic false positive test and one actually due to latent syphilitic infection.

Primary syphilis in the female. Samuel R. Damon. J. M. A. Alabama, Montgomery, 10: 221-222, Dec. 1940.

Primary syphilis in the female is often overlooked because the patient is not examined. To draw blood for a serologic test only on contacts without making a physical examination or a dark-field examination is doing the patient and the public health an injustice. Serologic tests are rarely positive before the seventh day of the chancre, but even then the percentage of positives is low. Thus, a test may be negative and yet the patient may have a primary lesion.

Contacts of persons known to have syphilis should be given a physical examination when they present themselves to the physician. It is unnecessary to examine meticulously the cardiovascular and central nervous systems of syphilitic contacts. However, careful inspection and palpation are essential. The skin and mucous membranes should be looked over for signs of lesions, and the lymph nodes should be palpated for signs of local or general lymphadenopathy. Accessible lesions should have serum collected from them for a dark-field examination. If there is glandular enlargement puncture of the gland should be performed to obtain the serum if the lesion is inaccessible. Every female contact of a syphilitic person should have a vaginal examination. This should include a speculum examination as well as inspection. To inspect the vulva only will in many cases overlook existing infections since chancres in women are on the cervix in about 44 percent of the cases.

Spontaneous subcapital hip fracture occurring in tabes dorsalis. Richard C. Batt and Aubrey O. Hampton. Bone & Joint Surg., Boston, 22: 146, Jan. 1940.

A study of all the cases of hip fracture seen at the Massachusetts General Hospital since 1920 revealed 5 cases of spontaneous fracture of the neck of the femur through the site of the epiphyseal line in adults. Three of these patients were known tabetics. Recognition of the fracture in another case led to a diagnosis of latent syphilis. A similar fracture was seen in only one other condition, namely, radiation osteonecrosis.

The condition is recognized by the following diagnostic criteria: (1) A break through the epiphyseal region between the femoral head and neck; (2) flocculent areas of calcification in the soft tissues surrounding the hip joint; (3) an apparent increased density of the femoral head; (4) a history of little or no trauma to account for the fracture. In view of the pathology and clinical aspects of tabes, a suspicion of tabes is justified when this fracture occurs.

Syphilitic osteomyelitis. H. A. Thompson and A. Mayoral. J. Bone & Joint Surg., Boston, 22: 203-206, Jan. 1940.

Syphilis of the bone may be congenital but it is more often a disease of acquired origin between the ages of 20 and 40. The roentgenographic appearance may simulate that of any bone lesion, and the diagnosis is doubtful until a biopsy is done. Gummatous osteomyelitis in adults leads to an extensive change in bone structure dependent upon bone destruction and bone formation, in which destruction usually predominates and produces irregular areas with mottling. This is illustrated by a reported case.

A male Negro aged 43 years was admitted to the U. S. Marine Hospital, Orleans, complaining of pain in the neck. In 1931 pain and stiffness had begun in his neck, and the condition then spread to other parts of his body. He had never been treated for syphilis. His blood

ctions for syphilis were strongly positive, but the spinal fluid Wassermann was negative. The diagnosis of syphilitic osteomyelitis was made on the roentgenographic findings in which extensive pathologic changes were found in the skull, upper cervical vertebrae, the iliac portions of the innominate bones, in the right humerus, the right clavicle, and the ribs, right side. The diagnosis of syphilis was not based on any one typical finding but on the diversity and widespread distribution of the lesions. The diagnosis was confirmed by biopsy. He was placed on antisyphilitic therapy and when last seen in January 1939 he showed marked improvement. He had no pain, was able to move his head through an arc of 70 degrees, and could flex the back to some degree.

note on the incidence of syphilis in alcoholics. Leo L. Orenstein and Walter Goldfarb. *Quart. J. Studies on Alcohol*, New Haven, 1: 442-443, Dec. 1940.

A search of the literature revealed no statistical material evaluating a correlation between alcoholism and syphilitic infection. An investigation was therefore made of 1,001 consecutive admissions to the alcoholic wards at Bellevue Hospital. The usual routine was employed in a detailed history of venereal infection or treatment and a blood Wassermann test. Since alcoholism may affect the Wassermann reaction, the blood was tested at the time of the patient's discharge from the hospital.

The distribution of the cases was 680 white males, 100 Negro males, 156 white females, and 65 Negro females. They are classified into groups with positive Wassermann reaction and negative history, positive Wassermann reaction and positive history, positive history and negative Wassermann reaction. Those with positive history or positive Wassermann reaction show percentages of 3.3 for the white males, 30 for the Negro males, 8.5 for the white females, and 55.3 for the Negro females. There is thus shown a

high incidence of syphilis in alcoholics among the Negro men and in both the white and Negro women. The finding that the frequency of infection in the women far exceeded that in the men, coincides with the general trend of behavior in the alcoholic patient. Contrary to general belief, men show a diminished sexual activity during intoxication; on the other hand, women expose themselves to greater sexual aggressions while intoxicated.

The use of an improved culture medium in the diagnosis of gonococcal infection in the adult female. S. Edward Sulkin and Eleanor Gottlieb. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 22-27, Jan. 1941.

The authors report the results of 2,050 examinations for the diagnosis of gonococcal infection in adult women, using the culture and smear methods simultaneously. Positive findings were obtained either by smear or by culture or by both methods in 284 (13.85 percent) of the total number of examinations made. Of the 284 examinations reported as positive, the cultural method was positive in 241 (84.8 percent), while smears were positive in 127 (only 44.7 percent). Therefore, the cultural method was 1.9 times more efficient than the smear method. In 43 (15.0 percent) of the cases of gonorrhea, intracellularly situated gram-negative diplococci resembling gonococci were found in smears, while corresponding cultures were negative. The combined smear and cultural method was 2.24 times more efficient than the smear method alone and 1.18 times more efficient than the cultural method alone. It is thus shown that the best procedure for the diagnosis of gonorrhea includes the use of the cultural as well as the smear method.

In this study culture medium recently described by Difco Laboratories, Inc., and recommended by Carpenter, Herrold, and Cox, McDermott and Hinton, was used. This medium contains an improved proteose-peptone and 2 percent beef

hemoglobin. This proteose-peptone hemoglobin agar can be made as easily as most culture media used in the diagnostic laboratory, and its availability in a dehydrated form has made the cultural method adaptable to laboratories which do not have facilities for preparing special media. The procedure used in the cultural method requires no special equipment other than an airtight container, a vacuum pump, a mercury manometer, and a cylinder of compressed carbon dioxide. The examination of cultures is a procedure no more difficult than that used in most other types of routine bacteriologic tests, particularly since the use of the oxydase test aids immensely in identifying colonies of the *Neisseria* group of bacteria. This test is especially valuable in examining cultures containing few gonococcic colonies obscured by the growth of other organisms.

The cultural method aids materially in establishing a definite diagnosis in cases with doubtful or negative microscopic findings. This is especially significant in specimens obtained from female patients, since a great variety of organisms comprising the bacterial flora may offer confusion. In this investigation of 71 smears showing extracellular gram-negative diplococci, 27 (38 percent) were proved positive by the cultural method, while 44 (61.9 percent) gave negative results. Also, of the 2,050 examinations made, 157 positive cultures were associated with doubtful or negative microscopic findings.

The cutaneous diagnosis of gonococcic infections. A further report. Budd C. Corbus and Budd C. Corbus, Jr. J. A. M. A., Chicago, 116: 113-115, Jan. 11, 1941.

A person infected with a specific organism is in a state of hypersensitivity to that organism as long as it remains within the body. The reaction of the skin to gonococcus toxin in persons affected with the gonococcus is a manifestation of allergy. During the past few years there has been considerable work done on this cutaneous manifestation of

allergy, 46 investigators having contributed to the subject.

A further study has been made by the authors, the Corbus-Ferry bouillon filtrate being used as an antigen and the bouillon medium as a control on 50 infected persons from public dispensary practices, 100 noninfected students as controls, and on 15 patients from private practice who had previously been cured with bouillon filtrate. Of the 50 patients with known infection of 2 or 3 weeks duration 90 percent gave positive results. Of 100 students 86 percent gave negative responses, and of the 15 patients from private practice 100 percent gave typical negative response. It was found that sulfanilamide therapy frequently modified the intensity or caused the temporary disappearance of the expected cutaneous response.

The authors believe that the test should be employed primarily as a diagnostic adjunct and not as a sole means of diagnosis. It should always be accompanied by routine measures, such as smear, culture, and complement fixation test when indicated. The test may be used as a criterion for cure; however, it is not reliable in cases in which intensive chemotherapy has been employed until 3 to 4 weeks after such treatment has been discontinued.

Symptoms of patients with heart disease and their interpretation. Soma Weiss. M. Clin. North America, Philadelphia, 24: 1295-1323, Sept. 1940.

During his discussion of symptoms Weiss states that aneurysm of the aorta per se causes dyspnea only if it presses on the trachea, bronchi or lung, possibly resulting in collapse of the lung. Otherwise the dyspnea associated with aneurysm of the aorta or with syphilitic aortitis is cardiac in origin, depending usually on an associated narrowing or occlusion of the coronary orifices or aortic insufficiency and secondary ventricular failure. Valid evidence is available that syphilitic involvement of the root of the aorta causes reflex dyspnea.

through irritation of nerve endings within the wall of the aorta. An instructive clinical demonstration of the fact that irritation of the nerve endings of the aortic arch does not cause reflex dyspnea is afforded by the behavior of patients at the onset of dissecting aneurysm of the aorta. In these persons, dyspnea is absent or slight, although the coats of the aorta are ripped from the valve to the iliac artery.

Early description of syphilis (Phirangi Roga) in Sanskrit texts. D. V. S. Reddy. *Indian J. Ven. Dis.*, Bombay, 6: 107-114, July-Sept., 1940.

In spite of the paucity of unimpeachable proofs from the ancient graveyards or from classical literature of the West or East, some believe that syphilis, in some form or other, existed in the eastern hemisphere before the discovery of America by Columbus. Most historians state that syphilis was imported into India by the Portuguese in the middle of the sixteenth century. Chakravarty, however, believes that syphilis existed in India previous to the voyage of Columbus.

Bhava Misra, distinguished Sanskrit pundit and professor of medicine in the upper Gangetic basin in the sixteenth century, wrote the earliest unmistakable and undeniable description of syphilis in his great classic, the *Bhava-Prakasa*.

To the Asiatics, the disease was known as "Frank's disease," because "Frank" was the general term for all Europeans. In India the translation of "Frank's disease" was "Phirangi Roga."

Reddy presents an extract from the *Bhava-Prakasa* describing the symptoms, complications, prognosis, and treatment of this disease.

Phirangi Roga is also mentioned in some other Sanskrit medical works composed over 300 years ago, including "*Rasapadhati*," by Bindu. Gode discussed the date of this work in a scholarly article in the *Poona Orientalist* (Oct. 1936, pp. 7-49) and concluded that it was composed between 1375 and 1650 A. D. This book contains a verse describing treat-

ment of syphilis with mercury, sulfur, and other drugs.

Rasapadhati is quoted in a later work, "*Aurveyada Prakasa*" of Madhava Upadhyaya. Gode assigns the latter work to the middle of the 17th century. It extols the curative properties of *Rasakarpura* (a mixture of mercurous chloride and mercuric chloride) as a sovereign remedy for syphilis.

TREATMENT

Combined artificial fever-chemotherapy in gonococcic infections resistant to chemotherapy. H. Worley Kendell, Donald L. Rose and Walter M. Simpson. *J. A. M. A.*, Chicago, 116: 357-363, Feb. 1, 1941.

The authors are reporting their study of 83 patients suffering from complications of gonorrhea, resistant or intolerant to chemotherapy, who have been treated with artificial fever, either alone or combined with chemotherapy. Of a group of 9 patients receiving fever therapy only, 12.5 percent were cured by a single 8-hour treatment at 106.6° F.; 62.5 percent of a group of 16 were cured after a single 10-hour treatment at 106.6° F.

Of 16 patients who received sulfanilamide intravenously in a dosage of $\frac{3}{4}$ grains (0.05 gm.) per pound of body weight immediately before fever treatment, only 13 (81.25 percent) were cured by a single 10-hour session. Eleven patients were given promin by intergluteal injections of 5 gm. every 3 hours during treatment, or a total of 20 gm., and of this group only 7 (63.6 percent) were cured in a single fever session.

All of the 31 unselected consecutive patients treated with sulfanilamide or promin (dextrose sulfonate) during 18 hours before a single 10-hour fever session at 106.6° F. were cured. These drugs were begun at 2 p. m. on the afternoon preceding the long treatment and given at 4-hour intervals, a total of 140 (9 gm.)

or 160 (10 gm.) grains of sulfanilamide (according to whether the patient weighed 150 pounds or over) being given by mouth, or a total of 25 gm. promin was given intramuscularly. Neither drug was given during treatment.

From this study it appears that, when combined with artificial fever, the effectiveness of chemotherapy (sulfanilamide or promin) is influenced by the time-dosage relationship with respect to fever treatment; when administered for 18 hours preceding the fever treatment, the effectiveness is much greater than when administered immediately prior to or during the treatment.

It was found that a 10-day period of intensive sulfanilamide therapy prior to fever therapy is without value in sulfanilamide-resistant patients, provided none of the drug is present in the body fluids at the time of the fever treatment.

The combination of a single 10-hour session of artificial fever therapy with the administration of adequate sulfanilamide or promin for 18 hours prior to the fever treatment appears to be the procedure of choice in the treatment of chemotherapy-resistant gonococcal infections.

Psychosis due to sulphanilamide. Rudolph B. Toller. *California and West. Med.*, San Francisco, 53: 266-267, Dec. 1940.

A case of toxic psychosis following prolonged use of sulfanilamide is reported. Premonitory symptoms were elation and excitement. After withdrawal of the drug a confused delirious excitement occurred, with delusions of persecution, hallucinations, and fear. Recovery occurred upon withdrawal of the drug.

The patient was a 22-year-old white man, who began treatment on December 11, 1939, for acute gonorrheal urethritis. He took 80 grains of sulfanilamide daily for 2 days, 60 grains daily for 2 days, and 40 grains daily for the next 41 days. During the last few days of this period his friends noticed a change in person-

ality. He was mildly elated, overactive, talkative, and argumentative. The symptoms disappeared when the drug was continued for 1 week. Sulfanilamide, 40 grains daily, was then resumed and continued for 2 weeks. After a rest period of 1 week it was again instituted because the urethral discharge had again become profuse. The dosage was 80 grains daily for 2 days, 60 grains daily for 2 days, and 40 grains daily for the following 27 days. About 8 days before the final dose the patient became overactive, talkative, and argumentative. He gradually became more restless and was unable to sleep. On March 25, 1940, mild persecutory delusions and auditory hallucinations developed, and the patient was fearful and apprehensive. He had no recollection of what happened from March 28 until April 9, 1940. The period of mental disturbance lasted 11 days. The patient received a total of about 3,840 grains of sulfanilamide in 101 days.

In subsequent interviews the patient was able to recall some of his psychotic experiences, but they were never clear and seemed dreamlike. His intellectual capacity was average for his station in life, and he had never before had a mental illness.

Brown, Thornton and Wilson studied the toxicity of sulfanilamide in 100 patients, observing mental depression and delirium in 2. Both effects were due to the drug.

Bannick believed that the toxic manifestations were on a basis of sensitivity and idiosyncrasy. Garvin noted mental symptoms after long administration of sulfanilamide or following the administration of smaller doses. He cited a case of a young girl, who, 10 to 15 minutes after receiving 1.3 gm. of sulfanilamide, became so irrational, disoriented and excited that she required full restraint. This occurred after each dose of the drug and usually lasted 2 or 3 hours. Fisher reported two cases of encephalomyelitis after small doses of the drug and he believed these patients were more than ordinarily susceptible to the drug.

Hogan and McNamara reported a case in which toxic symptoms occurred after the drug had been discontinued. In Danger's case mental symptoms developed days after the drug had been discontinued.

Headaches, dizziness, and lethargy may be premonitory symptoms, but Ottenberg does not believe that they are precursors of the more serious toxic symptoms. They may, however, develop into a more serious mental condition.

The mental symptoms are nonspecific and, as in other toxic psychoses, are dependent on the personality of the person. In most cases mental confusion and disorientation were reported as present, some patients were retarded, depressed, and negativistic, others exhibited bizarre behavior, and still others were maniacal. Delusions and hallucinations were present, usually of a persecutory and fear-motivated nature.

Myopia after use of sulfanilamide.
Emory A. Rittenhouse. *Arch. Ophth.*, Chicago, 24: 1139-1143, Dec. 1940.

The author reports a case of myopia following the use of sulfanilamide for syphilis, and he reviews the literature on the subject of myopia following the use of sulfanilamide. In all cases the condition cleared up following the discontinuance of the drug.

This toxic reaction has occurred in connection with sulfanilamide treatment of trachoma, pneumonia, sore throat, and gonorrhea. Transitory myopia has also occurred as a result of influenza, diarrheal conditions, icterus, acute inflammatory diseases, acute polyarthritis, arsenical therapy, alkalinity therapy, and diabetes mellitus.

It is possible that the rapid absorption of the drug can affect a transformation of the salt and water metabolism in the organism and thus make for a change in the lens which would be responsible for the disturbances of refraction. There may be a toxic irritation of the parasympathetic fibers of the ciliary muscles. In most of the cases the patient used the drug during one course of treatment

with impunity, the myopia developing during the next course of treatment. This warrants the conclusion that a sensitivity to the drug might be developed.

Despite the difficulty of deciding on the actual mechanism, the rapid onset after taking the drug and the apparent recovery after stopping the medicine seem definitely to indict sulfanilamide. However, good prognosis, with no apparently bad after-effects, is reassuring to all concerned.

Reactions to tryparsamide therapy.

W. G. Downs, W. McDermott and Bruce Webster. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 16-21, Jan. 1941.

During the period from October 1936 to October 1939, 5,353 injections of tryparsamide were administered to 223 patients with syphilis of the central nervous system at the syphilis clinic of the New York Hospital. Tabes dorsalis was present in 71; 16 had general paresis, 8 had taboparesis, and the remainder had some form of meningovascular or asymptomatic neurosyphilis. The fundi of all patients were examined by a member of the clinical staff, and in addition visual field and fundus examinations were performed in the Department of Ophthalmology of the New York Hospital on each patient before beginning therapy. The patients were questioned for visual symptoms by the physician before each of the first 8 or 10 injections, and subsequent fields were obtained immediately on appearance of any symptoms or routinely at approximately 3-month intervals as long as the patients were receiving the drug.

The majority of the patients were started on an initial dose of 1 gm., a second dose of 2 gm., and a third of 3 gm., and were then continued on 3 gm. weekly. A few were started on 3-gm. doses. No doses larger than 3 gm. and no intervals of less than a week were used.

Visual reactions occurred in 93 patients, 41 (44 percent) of which were subjective only and were accompanied by no demonstrable changes in the visual

fields. Visual field contractions were demonstrable in 52 (56 percent) of the visual reactions.

Of the 41 patients, 32 had their reactions early in the course of therapy, during the first 10 doses of tryparsamide, and by far the largest number of these occurred between the thirtieth and sixtieth injections. Thirty-one of the reactions occurred with a schedule of 1-2-3 gm. and 38 of the reactions with a dosage of 3 gm. After a rest period from tryparsamide, usually of several months, treatment was reattempted in 14 cases. Treatment was continued successfully in 8 of these cases, but 5 patients had further subjective reactions, all occurring between the third and fifth injections of the drug on the new course. One patient lapsed from treatment shortly after reinstitution of therapy.

Objective reactions, with definite contraction of the visual fields when compared with those preceding therapy, occurred in 52 patients. The appearance of pallor of the nerve was noted in some cases but was not considered as objective evidence of visual damage if unaccompanied by visual field changes.

Mild objective reactions, characterized by slight but definite temporary encroachment upon the visual fields (usually most marked in the nasal portion of the field) were noted in 20 patients. Moderately severe visual reactions, characterized by marked constriction of the visual fields but not in most cases permanent or severe enough to cause disability, were noted in 27 cases.

Severe reactions, marked by sudden complete or almost complete loss of vision, occurred in 5 patients. Some return of vision occurred in all these cases within a few weeks, but they were all left with extensive and permanent contractions of the visual fields of such a degree as to cause marked disability. Of these disabling reactions, 4 occurred early in the course of therapy, 2 after the second, 1 after the fifth, and 1 after the sixth injection. Two of the reactions occurred after 2 gm. of tryparsamide, 3 after 3 gm.

None of these patients was given further tryparsamide therapy.

Nitritoid reactions occurred in 30 (percent) of the total number of patients. 80 percent of these reactions occurred late in the course of therapy.

Five patients consistently complained of nausea and vomiting following tryparsamide, in some cases after relatively small (1 gm.) doses of the drug. 7 patients who had had dermatitis due to trivalent arsenicals developed similar dermatitis after tryparsamide therapy. No patient developed a dermatitis from tryparsamide alone. One patient had mild jaundice, with an icteric index of 25. The jaundice cleared rapidly. 1 patient also had diabetes mellitus and was suspected of having Laennec's cirrhosis of the liver. Seven patients had both visual and nitritoid reactions, 1 had visual and gastrointestinal reactions.

As a result of repeated reactions, tryparsamide was discontinued in 92 (percent) of the 223 patients.

Stilbestrol-induced gynecomastia in male. Charles William Dunn. *J. M. A., Chicago*, 115: 2263-2264, 1940, 28, 1940.

The therapeutic action of stilbestrol on the human being is under investigation by the Council of Pharmacy and Chemistry of the American Medical Association.

One of the established biologic effects of the naturally occurring estrogen is their growth-stimulating action on certain tissues and organs, one of which is breast tissue. It has also been experimentally established that when estrogenic substance is administered in sufficient amounts it has an inhibitory effect on anterior pituitary lobe trophic functions, among which are the production of growth hormones and the gonadotropic factor. A limited amount of clinical evidence supports these experimental observations.

The production of breast development in the female by the administration of natural estrogenic substance has been reported. The author has seen premature breast development in a girl 6 years

with gonorrheal vaginitis treated with stilbestrol. Neither hypodermic nor suppository estrogenic therapy could be administered because of the child's physical resistance to these forms of treatment. He was given 3 drops of stilbestrol solution (1 mg. per cc.) daily. After 6 weeks of stilbestrol therapy a mass approximately 2.5 cm. in diameter, and 1 cm. in thickness appeared beneath the nipple on both breasts. At this period of therapy the vaginal discharge had disappeared. The present report concerns a male sexual criminal aged 27 years to whom 30 mg. of stilbestrol had been administered orally over a period of 96 days, producing a marked bilateral gynecomastia. Physical examination revealed a firm, sensitive nodule beneath the nipple of each breast. The physical characteristics of the breast tissue reaction of stilbestrol and the naturally occurring estrogenic substances are markedly dissimilar in that the stilbestrol-induced mammary tissue growth is harder, firmer, and denser, and its rate of resolution after discontinuance of therapy is markedly retarded. The author assumes that the therapeutic effect has resulted directly from depression of the anterior pituitary gonadotropic function.

Present-day treatment of gonorrhea with fever therapy. A. I. Mann. *Am. J. Syph., Gonor. & Ven. Dis.*, St. Louis, 24: 743-744, Nov. 1940.

When sulfanilamide established a reputation as a specific in gonorrhea, about 3 years ago, fever treatment for that disease became obsolete overnight. However, more extended use of sulfanilamide showed that it cured an average of 75 percent of cases only, that toxic reactions sometimes required its discontinuance, and that it might even cause death.

Sulfanilamide-resistant patients began to be returned for fever treatment. Balinger and coworkers reported on the combined use of fever and sulfanilamide in resistant cases. They combined ordinary dosage of sulfanilamide with three fever sessions, averaging 4 hours, on alternate days, at a temperature of 103° to 104° F.

They reported a small series, but all were cured. Other authors have since reported giving such treatment with successful results.

In this article, Mann states that after employing various combinations of treatment with sulfanilamide and fever, he has concluded that it is best to use gonococcus exterminating temperatures in those patients who are sturdy and who can stand such treatment. The discharge can usually be terminated abruptly with 2 days of sulfanilamide, 6.6 gm. (100 grains) daily, followed by 6 hours of sustained fever at 106.5° F. This treatment is well tolerated.

Gonorrheal arthritis has proved less responsive to such treatment in the author's experience. Complete alleviation or improvement is usually manifest, but within a month there is usually a relapse and the arthritis becomes an atrophic type.

On the question of autopyovaccination in the treatment of gonorrhea. J. Křeček. *Dermat. Wehnschr.*, Berlin, 110: 482-485, June 8, 1940.

In the treatment of 26 men with gonorrhea (22 acute cases, 7 with anterior and 15 with posterior urethritis, and 4 chronic cases, 2 with anterior and 2 with posterior urethritis) the following method was used: After cleansing an area of skin with alcohol, 10 x 6 cm. of this area was scarified, and pus obtained directly from the urethra of the patient was rubbed into this scarified area. This procedure was repeated after 3 to 4 days and was the only treatment given. Individual patients were vaccinated in this manner from 3 to 8 times. Two of them showed good improvement (both had acute posterior urethritis), 10 showed slight improvement, and there were 14 failures. In 2 cases with acute posterior urethritis, epididymitis developed. In one patient abscesses developed at the site of vaccination. Only slight elevations of temperature were observed following vaccination—from 0.2° to 0.5° C. with no noticeable effect on the patients' general condition.

In an attempt to explain the ineffectiveness of this type of therapy, the author points out that it is impossible to determine exactly the dosage of vaccine given, that the amount of pus obtainable decreases with the number of vaccinations, and that the pus used for vaccination does not contain gonococci at their best, in other words they probably have been weakened or killed.

A further contribution to the study of side and after effects of the newer chemotherapy of gonorrhea. W. Volavsek. *Dermat. Wehnschr.*, Berlin, 110: 513-523, June 22, 1940.

In a series of gonorrhea patients on uliron, disseptal C, and albucid therapy, porphyrin, urobilin, and bilirubin determinations were made on the urine, and in some cases the Takata-Ara as well as galactose tolerance tests were carried out. Control experiments were made on similar patients not receiving chemotherapy. The morning urine was tested and the period of observation extended over 15 to 20 days. Therapy with any of the above mentioned 3 drugs in the usual dosage resulted in a definite increase in porphyrin excretion. This increase was observed in most cases on the 1 to 2 days of drug administration. The values were higher during the second than during the first course of treatment. A patient with a skin eruption resulting from the drug did not have greater porphyrin excretion than the patients who had no side effects. Bilirubin and urobilin excretion were also increased, the increase occurring chiefly toward the end of the course of treatment. Galactose tolerance tests and the Takata-Ara test, which were carried out only in cases in which liver involvement was suspected, were occasionally positive in those patients whose bilirubin and urobilin excretion remained high for a long period of time (as long as 2 weeks) after discontinuation of therapy.

The author concludes that sulfonamide drugs produce transitory damage of the liver which is manifested by a functional disturbance. He cautions against fre-

quent repetition of treatment courses and advises that the diet be such as to protect the liver. In this connection the gift of cane sugar has been shown to have a protective effect.

The chemotherapy of gonococcic infections. I. Summary of experience with sulfanilamide. II. Investigation of the chemotherapeutic effect of sulfapyridine. C. J. Van Slyke, R. R. Wolcott, and J. F. Mahoney. *J. A. M. A.*, Chicago, 116: 276-280, Jan. 25, 1941.

I. During 1937 and 1938 studies were made of approximately 1,800 hospitalized male and female patients who were treated for gonococcic infections with sulfanilamide. These have been reported previously, and a summary only is given here.

II. A series of 300 cases, comprising 200 male and 10 female hospitalized patients and 81 male and 9 female outpatients, all of whom were treated with sulfapyridine, is reported. The cure rate approximated 85 percent for patients who had not received previous chemotherapy and 70 percent for those who had failed to benefit by earlier sulfanilamide treatment. The larger dosages (6 gm. a day) were not more efficacious than the smaller doses (2 gm. a day). There were fewer and milder toxic manifestations among those patients who received the smaller doses. The toxic reactions were not serious and were significantly less with sulfapyridine, than with sulfanilamide. Subclinical carrier states were not encountered among patients treated with sulfapyridine, which is in contrast to the results found from sulfanilamide therapy. Prolonged administration of sulfapyridine is not indicated; the therapy should be limited to 10 days or less. If the lack of laboratory facilities would curtail the use of the drug, sound clinical judgment alone may serve as a practical guide to the use of sulfapyridine in the treatment of gonococcic infections.

The authors believe that at the present time sulfapyridine appears to be the drug of choice which can be applied on a broad

basis to the control of gonococcal infections.

Renal complications due to sulfathiazole.

Curtis F. Garvin. J. A. M. A., Chicago, 116: 300-301, Jan. 25, 1941.

At the Cleveland City Hospital, of 54 patients with pneumonia treated with sulfathiazole, 33 (61.1 percent) had crystals of the drug in the urine. In a control series of 56 patients treated with sulfapyridine, 16 (28.6 percent) had crystals in the urine. This is probably explained by the fact that 10.1 gm. a day of sulfathiazole was required to produce a blood level of 5.8 mg. per 100 cc., whereas 5.1 gm. of sulfapyridine was sufficient to result in a concentration of 5.4 mg. per 100 cc.

The incidence of hematuria was 14.8 percent for the sulfathiazole treated group and 10.7 percent for sulfapyridine.

Fatal agranulocytosis from sulfathiazole. Putnam C. Kennedy and Maxwell Finland. J. A. M. A., Chicago, 116: 295-296, Jan. 25, 1941.

A case is presented in which the complication of acute agranulocytosis proved fatal following the administration of sulfathiazole. The patient, a woman aged 38, was admitted to the Boston City Hospital on June 23, 1940. A diagnosis was made of subacute bacterial endocarditis superimposed on rheumatic heart disease with mitral stenosis. On the fifth day of treatment with sulfapyridine (1 gm. every 6 hours) was begun, but because of severe nausea and vomiting sulfathiazole was substituted. At first the dosage was the same. The nausea and vomiting continued intermittently, and at the middle of the 3d week the dosage was changed to 1 gm. every 4 hours. Acute agranulocytosis apparently began during the end of the third week of treatment with sulfathiazole. The drug was stopped on the 28th day when it was found necessary to give a blood transfusion. The patient died suddenly the next day.

No other drugs known to produce this condition were used after treatment with sulfathiazole was begun, although sulfa-

pyridine had been given for 2 days previously. No past history of treatment with sulfonamide drugs was elicited. The exact cause or mechanism of the sudden death is not certain.

Acetylglycarsenobenzene in treatment of syphilis. Preliminary report.

William H. Guy, Bernhard A. Goldmann, George P. Gannon and Jacob Slone. Arch. Dermat. & Syph., Chicago, 42: 1046-1058, Dec. 1940.

Acetylglycarsenobenzene (3,4'-diacetyl-amino-4-hydroxyarsenobenzene 2'-sodium glycolate) has been studied for 2 years in the department of dermatology of the University of Pittsburgh. A selected group of 84 patients were treated by intramuscular injections (49 patients were dropped from the series because of irregular attendance). None of the group had ever received antisyphilitic treatment before, and the diagnosis of syphilis was confirmed by dark-field examination or by serologic test. A total of 2,100 doses of the drug were given, with 1,656 doses of bismuth compound and 1,432 of mercury. Acetylglycarsenobenzene injections (4-6 cc.) were given once a week for 6 weeks, followed by soluble bismuth, one injection a week for 6 weeks, and then by mercuric salicylate, one injection a week for 6 weeks.

The spirocheticidal activity of the drug was shown by its rapid effect on the spirochetes in the primary lesions and the prompt disappearance of secondary lesions. A reversal of serologic reactions from negative to positive after treatment was not observed, and clinical relapse did not occur. The data from the study showed therapeutic results approximately equivalent to those with mapharsen. As to the comparative therapeutic efficiency only years of continued use of the drug on a wider basis will yield convincing data. The authors believe that the fact of local tolerance to the intramuscular route is established by this study.

Nitritoid reactions did not occur, but exfoliative dermatitis was observed in a much greater incidence than with other known arsenicals. The authors did not

observe the high incidence of toxic manifestations other than dermatitis, which has been reported by a number of foreign observers, who used the drug under the trade name "solusalvarsan."

From these preliminary studies the authors believe that acetylglycarsenobenzene is not to be recommended for general use. The incidence of toxic manifestations, such as dermatitis, must be materially lowered. Possibly, as in the case of arsphenamine, the manufacturers will be able to lower the toxicity by a modification of the chemical formula, so that eventually the drug may be administered with reasonable safety as well as with therapeutic effectiveness.

In the discussion Robinson said he had been investigating this drug at the University of Maryland for 10 months. His conclusions after treating 88 patients agree with those of the authors. Among his patients there was 1 case of fatal hemorrhagic encephalitis. The drug has also been investigated at Johns Hopkins Hospital, Moore reported, and he confirms the reports from the other two hospitals. In the three clinics 235 patients have been treated and there have been 28 serious reactions, an incidence of nearly 12 percent. This is so far above that observed with other arsenicals that Moore feels it justifies the immediate abandonment of the use of this one.

Excretion of bismuth in the urine of patients treated with bismuth ethylcamphorate. Francis M. Thurmon and Norbert Benotti. *Arch. Dermat. & Syph.*, Chicago, 42: 1073-1082, Dec. 1940.

The authors made a study of the daily excretion of bismuth in the urine of 9 adult patients after the intramuscular administration of clinical doses of an oil-soluble bismuth compound (bismuth ethylcamphorate), each cubic centimeter of which contained 40 mg. of elemental bismuth.

Three patients had only single injections, receiving 40 mg., 80 mg., and 80 mg. of bismuth, respectively; 3 patients received the 40 mg. dose per week for 3 weeks, and 3 received the 80 mg. dose per week for 3 weeks. In 2 of the 3 cases which received the single injections, the daily average bismuth excretion per week showed a maximum during the first week and in the other case the average excretion remained practically the same throughout. In 4 of the 6 cases of multiple injections, the daily average bismuth excretion per week showed ascending levels each week, the maximum being attained in the 3d week; in 1 case, the maximum was in the 2d week, and in 1 case the excretion remained practically the same throughout.

One patient receiving a single injection of 40 mg. excreted 36 percent of the bismuth in the urine within 18 days, and patients receiving 80 mg. excreted 29 and 20 percent in 18 and 19 days, respectively. Three patients receiving 40 mg. of bismuth each week for 3 weeks excreted 48, 29, and 30 percent in the urine in 20, 21, and 21 days, respectively; and patients receiving 80 mg. excreted 26, 29, and 17 percent within 18, 21, and 21 days, respectively. One patient receiving a single injection of 40 mg. required an observation period of 73 days before the excretion of bismuth ceased.

Roentgenograms of the site of injection (gluteal muscle) at intervals varying from 5 hours to 60 days after the injection in all instances failed to show deposition of bismuth.

As judged by the average daily excretion of bismuth in the urine, the 2-cc. dose (80 mg.) of bismuth ethylcamphorate administered at 7-day intervals is sufficient to maintain a sustained circulation of bismuth over a sufficient period of time to fall within the accepted standards of therapeutic effectiveness.

The fecal excretion of bismuth is not reported.

ate congenital syphilis. Observations upon thirty-nine patients over 25 years of age at the time of first admission. Frank R. Smith, Jr. Am. J. Syph., Gonorr. & Ven. Dis., St. Louis, 24: 755-758, Nov. 1940.

As an addendum to a previous paper Bull. Johns Hopkins Hosp., 53: 231, (1933) on the treatment results in a group of patients with late congenital syphilis seen in the adult clinic of the Johns Hopkins Hospital, the author has prepared this more detailed study of 39 of the patients who were more than 25 years of age when first admitted.

In this group of 39, there was an approximately equal number of white and negro patients; 42 percent were male and 58 percent female, and the mean age on admission was 33.4 years. In 4 cases, it was definitely determinable that the first acute and noticeable manifestation of congenital syphilis developed after the age of 25 years. Of these, 3 patients had acute interstitial keratitis, and 1 had a gumma of the nasal septum (osseous syphilis) which had progressed to perforation. In the remaining 35 patients there was some scar or basic stigma, often unnoted by the patient, to designate an earlier appearance of lesions. About one-half on admission showed scars of old interstitial keratitis or an active recurrence, 5 had Hutchinson's teeth which had been recognized as peculiar by the patient, 9 had previous saddle noses with perforation of the palate, 1 had periostitis of the tibia, and 1 had eighth nerve deafness.

Three of the patients were more than 50 years of age. One 61-year-old woman showed scarring of interstitial keratitis, eighth nerve deafness, prominent bossae, and typical Hutchinsonian teeth. Another woman, 60 years of age, had perforation of the nasal septum, erosion of the soft palate, scars of interstitial keratitis, and adentia. A third, 52 years of age, had a complete destruction of the palate, saddle nose, blindness from scars of interstitial keratitis, and total deafness.

Three patients between the ages of 30 and 40 years all had the Hutchinsonian triad, with prominent bossae. Two had

old erosive processes of the palate, and one had definite rhagades.

Five of the 39 had received some kind of parenteral treatment before coming to the clinic, all for a previous attack of interstitial keratitis. The treatment had been discontinued when the acute symptoms had subsided. None were treated adequately. The other 34 had had absolutely no antisyphilitic treatment at any time in their lives.

The incidence of the various lesions in this group was as follows: Hutchinsonian teeth, 14; interstitial keratitis, 26; eighth nerve deafness, 15; Hutchinsonian triad, 5; saddle nose and perforation of the palate, 18; periostitis of tibia, 8; bossae, 10; gummas, 4; and other complaints, 13. There were 8 patients with both interstitial keratitis and eighth nerve deafness, but in whom the upper incisor teeth had been removed before admission. "Other complaints" included rhagades, underdevelopment, and mental deficiency.

Over 90 percent of the objective signs of late congenital syphilis are to be found in or about the structures of the head. In a full-fledged case the diagnosis may usually be made by a glance at the face.

The serologic test of the blood was positive on admission in 30 patients, negative in 9. Neither the amount of treatment nor the age of the patient seemed to influence the incidence of Wassermann-fastness (66.7 percent in the inadequately treated; 57.1 percent in the adequately treated). The spinal fluid, examined on admission in 16 patients, was negative in 14 and positive in 2. The latter showed no clinical signs of neurosyphilis.

An evaluation of the effect of antenatal antisyphilitic therapy on fetal mortality and on congenital syphilis.
L. V. Dill, H. J. Stander and C. E. Isenhour. Am. J. Obst. & Gynec., St. Louis, 40: 965-979, Dec. 1940.

The records of patients treated in the New York Hospital (Cornell University Medical School) and the John E. Berwind Free Maternity Clinic for the past 7 years were studied. The charts of 386 syphilitic patients in whom 453 pregnancies had

occurred were reviewed. All patients had received routine antenatal care in addition to the antisyphilitic therapy, and each patient had received more than one treatment for the suspected syphilis. Of these pregnancies 139 were in Negro and 214 in white women. The treatment at the in-patient department consisted mostly of continuous therapy with arsphenamine, alternated with courses of bismuth. Recently, combined mapharsen and bismuth therapy has been instituted. Autopsy was obtained on all but a few of the dead babies. All living babies were routinely referred to the pediatric department of the hospital and were seen at 3-month intervals. A group of 414 patients who had had 500 pregnancies were used as controls for the syphilitic series.

The 386 patients in the syphilitic series had had 1,160 previous pregnancies. The greatest loss of life in both groups occurred in the early abortion division. More than 80 percent of the pregnancies of syphilitic patients in the New York Hospital and 90 percent of the Berwind pregnancies terminated in living, term babies. With pediatric follow-up of more than 6 months, only 9 pregnancies could be found which resulted in babies which could definitely be called syphilitic, and all of these were subjected to treatment. Two babies subjected to treatment before the end of the first month of life had an immediate reversal of serology. There were 4 infants in whom the blood Wassermann failed to become negative even after 2 or 3 months and in one case it remained positive for 6 months. These children have shown no clinical evidence of syphilis and with no treatment have remained clinically and serologically free from the disease for more than 4 years.

The roentgenograms of the long bones were frequently in error in the diagnosis of congenital syphilis. Two to 4 percent of nonsyphilitic babies had placentas which were classified as syphilitic. In the cord Wassermann tests done on 6 of the syphilitic babies, only 1 was found to be negative and the Kline test was strongly positive for this. This reaction

was positive in 16 to 18 percent of the normal babies.

The determination of the effects of treatment except in relation to the number of syphilitic babies and the number of fetal deaths was not attempted. On one fetus was found to be syphilitic whose mother received more than 6 grams of an arsenical preparation. The occurrence of deadborn babies and neonatal deaths did not vary directly with the amount of treatment received.

No syphilitic babies were obtained in the group receiving treatment both prior to and during the pregnancy, even though minimal treatment was received in both instances. The higher percentages of syphilitic babies were noted in the younger age groups of mothers.

From this study it is seen that syphilis need no longer constitute a major cause of fetal mortality or a frequent disease of the newborn. Antenatal therapy greatly enhanced by treatment received prior to conception. A favorable outcome is made certain by the early institution of treatment, advanced age of infection and a negative serology.

Fixed eruptions due to arsphenamine

Louis Chargin and William Leifer
J. Invest. Dermat., Baltimore, 3: 44-463, Dec. 1940.

Fixed eruptions produced by arsphenamines are apparently identical in every respect with eruptions of a similar type produced by other drugs. The term "fixed" does not refer to the duration of persistence of the lesion nor to its residual pigmentation, but solely to the fact that a previously affected area can be reactivated by the drug in question.

This report covers 69 syphilitic patients in whom during the course of treatment with trivalent arsenicals fixed eruptions developed. In this group 1 patient had a double sensitivity to arsenicals and phenolphthalein, and 1 was sensitive only to antipyrine. Race seemed an important predisposing factor—79 percent occurring in the Negro, 19 percent in the white, and 2 percent in the yellow race.

Lesions were most common on the face and were also observed over the entire body except on the scalp, palms, and soles. The mucous membrane of the mouth was involved in 2 cases. In descending order of frequency, the precipitating drugs were arsphenamine, neoarsphenamine, silver arsphenamine, mapharsen, and trisodarsen. Lesions produced by one trivalent drug were activated by other trivalent drugs and also by some pentavalent drugs. Activations were only seen when the drug was given by the intravenous, oral, or intramuscular routes. Patch tests and photophoresis were consistently negative. Successful full-thickness autotransplants in 3 patients failed to react when the drug was readministered.

In spite of continued arsenotherapy, no case of exfoliative dermatitis or any other type of arsenical dermatitis was observed in a patient having fixed eruptions. Since all trivalent arsenicals do not produce the fixed reactions with equal frequency, it is possible to continue therapy uneventfully by a change of arsenical.

In the discussion, Abramowitz remarked that this work of the authors outnumbered all reports in the literature since Naegeli in 1917 first called attention to such lesions.

Mapharsen as an antisyphilitic arsenical.

Edward A. Levin. *California and West. Med.*, San Francisco, 53: 207, Nov. 1940.

The author reviews briefly some of the literature on mapharsen. He states that it is still an experimental drug, although admittedly it has had extensive clinical trial in the last 8 years. So far, it has apparently shown itself to be as effective as arsphenamine in the treatment of the various manifestations of syphilis, as evidenced by the disappearance of spirochetes from early infectious lesions, healing of early and late skin manifestations, reversal of serologic reactions, and prevention of syphilis in newborn infants. Although it probably will prevent the later complications if used adequately, about 20 years must pass before this can be definitely stated.

In over 5 million injections reported to date, only two fatalities have been reported. This is much less than would be expected from neoarsphenamine. It has been particularly noted that instances of blood dyscrasias, severe or exfoliative dermatitis, liver damage, and other serious and at times fatal reactions occurring with neoarsphenamine are very rare. No case of nitritoid reaction due to mapharsen has been reported.

Some patients cannot tolerate mapharsen without experiencing nausea and vomiting. Pain along the course of the vein and extending up the arm to the shoulder may also occur. While these are not serious reactions, they are disconcerting to the patient. The author states that, in spite of these minor reactions, and in view of its low toxicity, ease of preparation and administration, and the excellent results so far obtained, the further use of mapharsen as an antisyphilitic remedy is justified.

Syphilis in brothers. Transfusion syphilis; the occurrence of positive spinal fluids after a previously negative examination; therapeutic failure of two usually effective treatments for syphilis. Clarence S. Livingood and Herman Beerman. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 67-71, Jan. 1941.

The authors present the cases of two patients (brothers) in whom syphilis, derived accidentally from the same strain through blood transfusion, passed through a relatively similar series of events in spite of the use of different systems of antisyphilitic treatment in each case. The older brother, the donor of the transfusion, was given concurrent treatment with 40 neoarsphenamine and 47 bismuth salicylate injections over a period of 14 months. Because his blood serologic tests were persistently positive he was given 20 injections of boiled milk, 7 injections of bismarsen, and 8 injections of bismuth salicylate during the next 20 months. The younger brother, the recipient of the blood transfusion, was given 50 injections of bismarsen in 15 months with an addi-

tional 15 injections of bismarsen and 2 injections of bismuth salicylate in the next year.

In both patients abnormal spinal fluids developed after they had been given what is usually considered adequate antisyphilitic treatment, and following previously normal spinal fluid tests.

These patients serve as an example of the dangers involved in using a transfusion donor whose syphilitic status has not been determined. They are exceptions to the rule that negative spinal fluid examinations in early or latent syphilis are favorable prognostic signs.

If each case had been studied individually, the failures would have been ascribed to the drug used. The circumstances attending these cases have made it possible, for practical purposes, to eliminate the drug and to incriminate the host or the spirochetal strain as responsible for the failures.

A case of peripheral neuritis following disulfanilamide treatment. Edward R. Hodgson. *Journal-Lancet*, Minneapolis, 61: 22-23, Jan. 1941.

From a review of reported cases it seems fairly certain to the author that disulfanilamide (sulfanilyl sulfanilamide, disulon) and dimethyl disulfanilamide (uliron, disseptal, D373) result in the development in some individuals of a rather consistent type of peripheral neuritis. Hodgson reports a case which he feels is an example of this manifestation.

The patient was a 24-year-old graduate student from Turkey. In November 1938 he started taking disulon. He took 60 grains daily for 1 week, followed by 2 weeks with no treatment, and then 30 grains daily for another 3 weeks, followed by another 2 weeks without treatment. He started a third course of 30 grains daily but this was discontinued in a few days. He probably took about 1,000 grains (66 grams) in 2 months. In January 1939, symptoms appeared of weakness in the legs with pain after moderate exertion, and weakness of the hands which progressed so that he could not hold a pen

or shave himself. Examination showed nothing abnormal; blood sulfanilamide was negative. In May there was some improvement. Skull films were normal as was the spinal fluid, blood serology and blood chemistry. He was given vitamin B₁ intramuscularly, brewer's yeast and thyroid. Thyroid was stopped after 1 month but he continued the yeast tablets. When the patient was seen in October all motions of the hands were normal and strength was good.

PATHOLOGY

Aneurism of the aorta. A clinical pathological analysis of 127 necropsies. Michael A. Ogden. *Urol. & Cutan. Rev.*, St. Louis, 44: 731-735 Nov. 1940.

This study is based on 9,000 consecutive necropsies performed between 1931 and 1938 at the Charity Hospital, New Orleans. There were 418 syphilitics in the series; aortic aneurysms developed in 127 (30 percent). There were 2 cases in which the aneurysm was not due to syphilis. Rupture occurred in 55 of the 127 aneurysms. The incidence of rupture was 55 percent among the white patients and 40 percent among the Negroes.

The average duration of the syphilitic infection in 21 patients was 18 years, the shortest period being 6 months and the longest 35 years. Of the 127 aortic aneurysms, 116 were saccular, 2 fusiform, and 9 dissecting. There were 15 aneurysms of the abdominal aorta, 8 of which ruptured. The thoracic aorta was the site of the aneurysm in 112 cases—35 in the ascending portion, 12 of which ruptured; 57 in the arch, 22 of which ruptured; 20 in the descending portion, 12 of which ruptured.

Microscopic examination of the aortic wall usually showed that all three layers were affected. The whole adventitia was swollen, congested, edematous, and considerably thickened. Marked vasculariza-

ion with destruction of muscular and elastic tissue with a variable degree of replacement fibrosis was found in the media. In nearly all cases of syphilitic aortitis marked arteriosclerotic changes were found in the aortic wall.

Dyspnea was the most constant symptom. When pain was present in the chest it was chiefly substernal; abdominal pain radiated to all parts of the abdomen. The symptomatology of ruptured aneurysm sometimes simulated that of malignant abdominal tumor, perforated peptic ulcer, or ruptured ectopic pregnancy.

The Wassermann reaction was positive in 41 out of 84 cases. In 55 cases death was the result of rupture of the aortic aneurysm; in 9 cases it was due to pressure of the aneurysm on the trachea or to pulmonary atelectasis. Three died from occlusion of the coronary ostia due to extensive syphilitic aortitis, 34 from heart failure, and 1 from gumma of the heart.

fatal aplastic anemia following the use of mapharsen. Report of a case. D. Kirkham and Martin Perlnutter. *Arch. Dermat. & Syph.*, Chicago, 43: 111-115, Jan. 1941.

No case of aplastic anemia nor of death due to mapharsen appeared in the literature until November 1939, at which time Wein and Wise reported the case of a woman who died with a typical picture of aplastic anemia one month after her 5th injection of mapharsen.

A 24-year-old Italian-American housewife was admitted to the Long Island College Division of Kings County Hospital on Nov. 11, 1939 for treatment of vaginal bleeding of 2 weeks' duration. The Wassermann reaction of her blood had been found positive and antisymphilitic treatment had been begun 7 months previously. The first course consisted of 10 injections of 0.2 gm. of thiobismol and 1 of 0.04 gm. of mapharsen. A second course consisted of 9 doses of 0.2 gm. of bismuth subsalicylate and 8 doses of 0.06 gm. of mapharsen. One month before admission the third course was started.

She received 9 injections of 0.2 gm. of bismuth subsalicylate in oil and 1 dose of 0.03 gm. of mapharsen. The total amount of mapharsen administered in all courses was 0.97 gm. Two days prior to admission she complained of a sore throat. There was no history of fever or of bleeding from other orifices. Her temperature ranged between 101° and 105° during the 8 days of observation; on the 6th day profuse vaginal bleeding reappeared. She died suddenly but not, so far as could be ascertained, because of hemorrhage. Among the autopsy findings were aplasia of the bone marrow, splenomegalia, hemorrhagic endometrium, multiple hemorrhages in the viscera and retroperitoneal tissue and subcutaneous emphysema.

The authors believe that the only obvious etiologic factor for this case of fatal aplastic anemia was the administration of the 0.9 gm. of mapharsen, which was the total dosage given in 3 months.

LABORATORY RESEARCH

Sulfathiazole in blood and urine. F. William Sunderman and D. Sergeant Pepper. *Am. J. M. Sc.*, Philadelphia, 200: 790-795, Dec. 1940.

The authors state that the methods currently employed for the analysis of sulfathiazole in blood are considered inadequate, since recovery of the drug when added to whole blood is uniformly low. In this paper they report observations regarding the difficulties encountered in the analyses and offer a procedure of analysis applicable to clinical purposes. They also report the results of studies relating to the excretion of the drug in urine, its solubility, and crystal structure, since the greatest danger in the use of the drug seems to be the occurrence of crystalline concretions in the urinary passages.

When they applied methods for the analysis of sulfanilamide in whole blood to the measurement of sulfathiazole, the authors found that recovery of sulfathiazole in whole blood averaged only 86 percent of the theoretical. When they used serum instead of whole blood, the loss of sulfathiazole was much less, averaging only about 3 percent. Therefore, they believe that analysis for sulfathiazole should be made with serum instead of whole blood. A procedure for analysis in serum is suggested in which an arbitrary correction for the loss is made in the final calculation.

Since both sulfathiazole and its acetyl derivative are about twice as soluble in urine of pH 7.6 as in urine of pH 5.6, it may be inferred that when crystalline concentrations due to sulfathiazole therapy threaten, an effort should be made to keep the urine alkaline and to secure a large urinary volume.

The toxicity, absorption and chemotherapeutic activity of 2-sulfanilamido-pyrimidine (sulfadiazine). W. Harry Feinstone, Roger D. Williams, Robert T. Wolff, Evelyn Huntington and M. L. Crossley. *Bull. Johns Hopkins Hosp.*, Baltimore, 67: 427-456, Dec. 1940.

Sulfadiazine was investigated for its toxicity in laboratory experimental animals, for the rate and mode of absorption from oral administration and from subcutaneous administration of the sodium salt, and for its therapeutic effect in various experimental infections in mice.

Based upon blood concentrations, the acute toxicity of sulfadiazine for mice was found to be about 175 to 200 mg. per 100 cc. as measured by the parenteral administration of the sodium salt. The administration of toxic doses of the sodium salts of sulfathiazole and sulfapyridine resulted in blood concentrations of about 80 and 65 mg. per 100 cc., respectively.

Based upon blood concentrations in chronic toxicity experiments, sulfadiazine produced less tissue damage in monkeys than sulfathiazole or sulfapyridine did.

This may be partly explained by the fact that the solubility of acetyl sulfadiazine in urine is much higher than that of the acetyl derivatives of sulfapyridine and sulfathiazole, and that sulfadiazine is not conjugated to the same extent as sulfapyridine.

The blood concentration resulting from given doses of sulfadiazine was about 10 times as high in monkeys as the concentration resulting from similar doses of sulfapyridine. Mice showed blood concentrations 4 to 5 times as high with sulfadiazine as with sulfanilamide, sulfapyridine, or sulfathiazole at the same drug intakes. In the dog, the absorption of sulfadiazine, following a single dose, was not markedly different from that of sulfapyridine. Rabbits showed a great deal of individual variation.

The absorption of sulfadiazine by mice is rapid and concentrations of the drug are maintained for more than 24 hours. The peak of absorption by some monkeys was not reached until 4 or more hours and the blood stream contained the drug 36 hours after the dose. Sulfadiazine has a high therapeutic activity in experimental pneumococcal, streptococcal, and staphylococcal infections of mice.

Is there a correlation between the clinical course and curability of gonorrhea and the A-, C-, and D-strains? H. Neumann and J. Altmeyer. *Dermat. Wehnschr.*, Leipzig, 111: 706-709, Aug. 17, 1940.

In order to determine whether there is a correlation between the clinical course and curability of gonorrhea and the 3 different strains of gonococci, the cases treated exclusively with silver preparations during the years 1935 and 1936 were reviewed. This group consisted of 155 men (111 with A, 32 with C, and 12 with D gonococci) and 344 women (216 with A, 90 with C, and 38 with D gonococci). In the group of men it was observed that 16 percent more of the A and C patients remained free from complications and recurrences than the D patients. When the course of the disease was prolonged, it

are more commonly due to complications in the A and C patients and to recurrences in the D patients. The complement fixation reaction for gonorrhea was positive in 87 percent of the A and C male patients and was negative in all 12 of the D male patients, in spite of the fact that 3 of the D patients had complications.

Also among the women the percentage of cures was higher (7 percent) in the A and C patients than in the D patients. There were no other essential differences, however.

In a group of 86 patients treated with sulfonamides it was observed that the D patients showed the best response to treatment. This good effect of sulfonamides in D patients is assumed to be due to special antigenic properties of the D bacilli.

Influence of dietary protein on the toxicity of sulfanilamide. M. I. Smith, J. D. Lillie and E. F. Stohman. *Public Health Rep.*, Washington, **56**: 24-29, Jan. 3, 1941.

After the authors' work showing that the chronic toxicity of ingested selenium was greatly influenced by dietary protein, they became interested in determining whether a similar relationship might not exist with reference to subacute or chronic intoxication with sulfanilamide. Experimental work, therefore, on albino rats was carried out.

It was found that a low protein diet (10 percent) increased the susceptibility of rats to orally administered sulfanilamide by increasing the mortality rate and the incidence of anemia as compared with similarly treated rats on a diet containing 30 percent protein. Supplementing the low protein diet with cystine to the level contained in the 30 percent protein diet had no effect, while a similar supplement of cystine plus methionine decreased the mortality rate but not the incidence of anemia. Examination of the blood sulfanilamide levels suggests the possibility of greater retention of the drug in animals on the low protein diet.

Histologic examination of the tissues failed to reveal specific damage attributable to low protein sulfanilamide treatment. Renal concretions and fatty metamorphosis of the liver were observed in animals on low protein diet irrespective of sulfanilamide treatment. The former appears to be preventable by methionine but not the latter. A slight focal interstitial nephritis was present in about a third of the sulfanilamide-treated animals irrespective of diet.

Splenic pigmentation and myelosis were most pronounced in the sulfanilamide-treated animals on the high protein diet suggesting increased activity of hematopoietic organs to compensate for the blood destruction.

Effects of continued administration of sulfanilamide on the blood. Arthur P. Richardson. *J. Pharmacol. & Exper. Therap.*, Baltimore, **70**: 370-377, Dec. 1940.

Since damage to the blood is one of the outstanding complications accompanying treatment of bacterial diseases with sulfanilamide and its derivatives, it seemed important to assess the drugs for such toxic potentiality. Accordingly white mice were fed a diet of powdered Purina Dog Chow containing appropriate concentrations of sulfanilamide, and studies were made.

The continued administration of sulfanilamide in the diet to mice produced a secondary anemia resembling closely that resulting from clinical medication. The anemia was characterized by reticulocytosis, increase in mean corpuscular volume of erythrocytes, development of Heinz bodies, and marked deposits of hemosiderin in the spleen, the leukocytes and platelets being unchanged. A given concentration of sulfanilamide produced maximum blood changes within 2 to 4 weeks, beyond which period of time continued administration of sulfanilamide produced no further anemia. Splenectomy had no effect on the development of anemia or cyanosis.

Anticomplementary action of serum and the Wassermann reaction. W. Hayes and H. Sachs. *J. Path. & Bact.*, London, 51: 455-458, Nov. 1940.

Serums with anticomplementary action so strong as to prevent the reading of the Wassermann reaction are seldom encountered. Jersild and Pedersen (1938) have reported the finding of only 15 to 20 serums with a distinct anticomplementary action among 125,000 blood samples tested yearly in the State serum Institute, Copenhagen. According to these authors the anticomplementary action developed only after heating at 54 to 55° C. and was intensified on heating at higher temperatures. Their observations apparently relate to nonsyphilitic serums.

The rarity of strong anticomplementary serum action may, therefore, justify the reporting of a serum from a case of tertiary syphilis which showed, on repeated examinations, such marked activity after inactivation for one-half hour at 55° C. that it was never possible to read the Wassermann reaction. The Kahn test was positive on each occasion.

It appeared interesting from the practical point of view to find out whether the Wassermann reaction might be performed on this serum in the unheated state. It was, therefore, examined before and after heating at 55° and 65° C. It was found that the strength of the Wassermann reaction was decreased by heating the serum at 55° C., although its anticomplementary action only developed after this treatment. This lack of parallelism demonstrates that the anticomplementary action and the ability of the serum to give a positive Wassermann reaction are quite independent of one another. The Wassermann reaction could be carried out upon the unheated serum since the anticomplementary action only developed on heating.

It was also possible to perform the reaction on the heated serum by using the fluid remaining after precipitating the anticomplementary globulins with dilute HCl. Inhibition of the flocculation reac-

tions and a distinct increase in precipitability by very dilute HCl coincided with the development of anticomplementary action on heating the serum.

Methods for the isolation and cultivation of treponemes, with special reference to culture media. Clara Kast and John A. Kolmer. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis 24: 671-683, Nov. 1940.

The successful cultivation of *Treponema pallidum* in a form virulent for rabbits is still an unsolved problem. Kast and Kolmer, in this paper, describe methods for the successful isolation of *Treponema microdentium* and *Treponema macrodentium*. They describe the preparation of 18 different media and the influence on the cultivation and morphology of three strains of *Treponema pallidum*, *Treponema microdentium*, and *Treponema macrodentium*. They hope that from this work will finally evolve a method for the cultivation of virulent *Treponema pallidum*.

The three strains of *Treponema pallidum* used were (a) the Noguchi culture (No. 1020) cultivated by Noguchi in 1917, (b) the Nichols-Hough strain cultivated by Kast and Kolmer in 1933, and (c) the Kroo culture furnished by Wadsworth in 1933.

The *Treponema microdentium* was isolated from material obtained from a severe case of spirofusillar gingivitis (pyorrhea alveolaris). The *Treponema macrodentium* was isolated from a case of Plaut-Vincent's angina in 1935.

Treponema microdentium is the thinnest of the five organisms and is very similar in morphology to virulent *Treponema pallidum* from human or rabbit lesions. *Treponema macrodentium* and the Kroo strain of *Treponema pallidum* are somewhat thicker; the former is more flexible and more actively motile than the other strains and changes its curves more when motile. The Noguchi strain has wider curves and grows into longer forms than the Kroo strain. The curves of the Nichols-Hough strains are wider than those of the Noguchi strain. Since c

ated by Kast and Kolmer in 1933, they gradually become longer and thicker. Cysteine broth with ascites fluid has been found the best fluid medium for the growth of the Noguchi and Nichols-Hough strains. The best semisolid medium for the growth of these strains has been coagulated liver broth and ascites fluids. Coagulated horse serum and heart infusion broth (1:2) have proved best for maintaining stock cultures. The cultural characteristics of the Nichols-Hough strain are practically the same as those of the Noguchi strain.

The Kroo strain of *Treponema pallidum* grows best in media prepared with liver broth. Coagulated liver media have been found best for stock cultures, in which the organisms can be preserved for about a year at 35° C.

The strain of *Treponema microdentium* grows best in a fluid medium of liver broth; also in neutralized rabbit kidney broth in tubes of 4.5 cc. of heart infusion broth plus 0.5 cc. of sterile defibrinated rabbit blood. The best solid media were those of ascites fluid plus neutralized beef agar and coagulated ascites fluid plus liver broth. These organisms multiply more rapidly than any of the other cultures of treponemes, giving good growths in 2 to 5 days and showing the motility at 35° C. Stock cultures can be maintained for several months at a temperature in media of neutralized beef broth or agar.

Treponema macrodentium did not grow in pure culture in a fluid medium when first isolated, but now it grows well in neutralized kidney broth, liver broth, glutathione broth containing sterile rabbit serum. Morphology is best preserved in neutralized kidney broth, while considerable autoagglutination occurs in liver broth and more when horse serum is used for enrichment than when ascites fluid is employed. Neutralized kidney broth and coagulated liver are the best solid media, and stock cultures have been maintained in the former over periods of many months.

All strains can be cultivated in anaerobic jars, but Kast and Kolmer believe that the use of vaseline seals is more convenient. The authors discuss in detail the preparation of the various culture media.

PUBLIC HEALTH ADMINISTRATION

The American Neisserian Medical Society. Address of the president, 1940. N. A. Nelson. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 1-6, Jan. 1941.

The author recommends that the objective of the American Neisserian Medical Society be stated as follows: "Through research, through the practice of medicine, through public health procedure, and through public education, to exterminate the gonococcus."

It is necessary to prove that the smear, as a diagnostic procedure, is worth only what it positively discloses; that in vulvovaginitis in children and in some adult female conditions even positive smears have no final significance; and that this laboratory procedure has little or no negative value.

Culture of the gonococcus is still largely experimental and confined to the more advanced bacteriologic laboratories. A generally acceptable and universally workable standard culture medium has not yet been developed. The oxydase test must apparently be interpreted with reservations and supported by fermentation tests in many cases. A practical method for keeping the gonococcus alive for transportation to a central laboratory has not yet been devised. Hundreds of laboratory technicians must be trained in the culture of the gonococcus; proficiency in general bacteriologic technics is not enough.

Since sulfonamide therapy has become so widely used, criteria of cure which do not include cultures are apparently worthless. Without cultures, therefore, it is impossible to evaluate these new drugs. It is already becoming apparent, where cultural studies have been made, that sulfanilamide is far less effective as a cure for gonococcal infection than it was at first thought to be, and that some of the newer drugs, such as sulfapyridine and sulfathiazole, are considerably more efficient. Should sulfanilamide be abandoned in favor of the newer drugs? Have any of these drugs been so fully evaluated that exact advice can be offered as to their relative usefulness?

The author believes there should be three qualities of membership in the American Neisserian Medical Society, as follows:

1. Those who are so situated and so inclined that they may do scientific and clinical research. They should make original investigations, report their findings, act as a guide in the stimulation of others to research, and advise concerning the practical application of their findings. They are the "pullers" of the load.

2. Those who can apply the results of research. They should repeat and either confirm or refute the results of those who have made the original observations. They should help to determine whether the results of research have practical applications. They should suggest the directions which further research should take. These may be called the "pushers" of the load.

3. Those who are so situated that they can do neither of these things but who are rich in practical experience and who are able to give encouragement and practical counsel. They may be called the counsellors and the cheer leaders of the Society.

The author suggests to the members of the Society: "If you can't pull, push! If you can't push, advise or cheer! If you can neither pull nor push, advise nor cheer, get out of the way!"

"A contribution to the enlightenment of the frequency of syphilis among warable officers and crews of the Danish mercantile marine." F. Reynr. *Acta dermat. venereol.*, Stockholm 667-673, Nov. 1940.

The author made a study of the records of 837 men in the employ of a Danish steamship company. Among these he found historical evidence of syphilitic infection in 13.2 percent. He compares incidence with the incidence of 4 percent found in the surgical ward of a Copenhagen hospital and that of 13 percent found in a ward of another hospital for chronic diseases. Male adults over 20 years of age were selected for examination in both of these hospitals. However, he excludes the cabin boys and a few others in obtaining the incidence of syphilis percent for the seamen. If this group is included, the incidence is 11.8 percent.

The incidence of syphilis among different groups of workers on the ship was as follows: Stokers, greasers, and messengers, 27.3 percent; stewards and deck officers 13.8 percent; engine officers 12.2 percent; deck officers 10.2 percent, and deck hands 7.8 percent. He attributes the comparatively low incidence among deck hands to their being much younger (many of them under 20 years of age) and to their short period of service. One fifth of the group of those who had been infected with syphilis had received their infection before the age of 20 years and more than one half of them before the age of 30 years.

The author points these findings out as being a problem for the Danish medical authorities and advises that steps be taken to make adequate treatment available for merchant seamen, regardless of the difficulties.

30,000 individual kits being prepared for blood tests for drafted men. *Michigan Pub. Health*, Lansing, 28 Nov. 1940.

Individual kits are being supplied to the Michigan Department of Health draft-board physicians for taking

specimens of men called for physical examination. These kits, sterile and sealed, are designed for ease and speed in taking blood specimens.

The 4-gram vial, antitoxin needle of .21 gauge, and self-sealing gum stopper make up the specimen kit. The physician plunges the short end of the needle through the stopper and the vial thus becomes a handle for inserting the needle into the vein. A short rubber tube with a rubber piece is connected with an ordinary hypodermic needle to the vial and by suction the physician produces a vacuum, the blood flowing into the vial. The suction needle is above the other needle so no contamination can result. When the specimen has been taken the needles are pulled out of the gum stopper, which immediately seals itself. An identification ink is fastened around the vial. Two kits are packed in one mailing tube.

The specimen kits are being assembled at a very low cost. Exclusive of the 1,000 kits being made up, 1,000 suction tubes with cotton protector and needle connections are being prepared.

The laboratory is planning two shifts of laboratory technicians to take care of the extra load anticipated.

Microscopic examinations for gonorrhea will also be done if requested by examining physicians.

Control of venereal diseases in California: Cooperation of druggists. California and West. Med., San Francisco, 3: 306, Dec. 1940.

Cooperation of druggists is proving a vital factor in the control of venereal diseases in California. Hundreds of patients have been referred to doctors and clinics since the State department of public health began its voluntary program of cooperation.

Starting in Alameda County in February 1940, the program has been completed in the following counties: Contra Costa, Imperial, Nevada, Sacramento, San Diego, San Joaquin, Sonoma, Sutter, and Yuba. It is nearing completion in Los Angeles County.

Pledges of cooperation had been made by 1,280 druggists up to November 1, 1940. Only 11 firms had refused to sign the pledge that they "will not sell medicines for the treatment of venereal diseases except upon order of a physician's prescription and will refer all patients to a physician or to a health clinic."

In response to a questionnaire, physicians in Alameda County reported that 122 patients had been referred to them by druggists since the educational program was concluded there. The Oakland city clinic reported that it had admitted 105 patients referred by druggists during the same period.

Applied common sense in national defense. Editorial. Ray Lyman Wilbur. J. Soc. Hyg., New York, 26: 430-431, Dec. 1940.

Our country takes on a new responsibility for the future in its peacetime conscription program. It must give adequate protection to the young men brought into military service from those perils associated with groups of men away from home ties and accustomed influences. From time immemorial every collection of soldiers has been sought out by those purveying to man's weaknesses and vices. Saloonkeepers, gamblers, and prostitutes head the list. To keep the men fit is much more than a moral question; for in many armies gonorrhea and syphilis have damaged more men than have the bullets of the enemy.

The American Social Hygiene Association fills in where the military authorities cannot act. It provides education for the recruit and for the public, provides experts to work with the police and civilian authorities, and is an agent of the free giver who wants to do his share in preventing disease and disaster. At no time has the need of emphasis upon the work of the Association been so important as today, with changing social customs and standards, with tens of thousands of places where alcohol is sold, with barmaids and "B" girls and the easy association of the young people of both sexes.

American Legion's National Child Welfare Division. C. B. Orth. Pub. Health News, Phoenix, No. 176: 1-4, Nov. 1940.

The American Legion's child welfare program has been built upon cooperation with standard child-caring and protective agencies. Its service and aid is for the benefit and best welfare of the child itself, and its slogan is "A square deal for every child."

Intelligent defense against disease is a plan of national defense that is beyond controversy. The American Legion is interested in national defense and in the future citizens of the country. Good health is a child's best assurance of becoming a desirable adult citizen.

The attack upon disease is broken down into assaults upon each infectious disease. The objective for the attack upon syphilis is: No baby born in the United States with syphilis by 1945 and a complete eradication of the disease in two generations. This is to be accomplished by (a) premarital examinations, (b) blood tests early in every pregnancy, (c) treatment facilities available to all, (d) education as to the necessity of continued treatment for all syphilitic expectant mothers, (e) laboratory services available for all physicians, (f) reporting all new cases, (g) free distribution of drugs and free treatment for the indigent, (h) tracing and isolation of infectious, noncooperative cases, (i) making provision for treatment and isolation (if necessary) of infectious transient cases, (j) cooperation between private physicians and public clinics, (k) continuing the educational program among medical and lay groups, (1) developing and popularizing a minimum standard of treatment for all food handlers, persons associated with children, nurses, physicians, and midwives, with prohibition of any found infected from continuing in that capacity until treatment is accepted.

Missouri gonorrhea control program. J. Missouri M. A., St. Louis, 38: Jan. 1941.

In cooperation with the U. S. Public Health Service, the State Board of Health of Missouri and the Committee on Control of Venereal Disease of the Missouri State Medical Association have deemed it advisable to make sulfathiazole available for the treatment of patients suffering from gonorrhea. This chemotherapeutic drug seems to give a high percentage of cures and has a relatively low toxicity. It will be made available on the same basis as is now being used to provide treatment for syphilis.

Sulfathiazole will be distributed to private physicians by full time county district health officers on the receipt of venereal disease report forms reporting cases of gonorrhea and requesting drugs for treatment. The plan of treatment is as follows: Oral administration of grains of sulfathiazole four times a day (60 grains a day) for a period of 5 successive days. A second course of drug is not advised in event of failure.

To facilitate the diagnosis in all cases of gonorrhea suspected or reported by a physician, urethral or cervical smears must be made and sent to the State board of health laboratory or other approved laboratories. The physicians of Missouri are urged to report all cases of gonorrhea coming to their attention in their practices.

Because the State board of health is financially accountable for all drugs purchased through their facilities with State and Federal funds, a treatment record and a special form must be kept in all cases in which drugs are furnished by the State board of health. These records are to be sent to the district or full-time county health officers at the completion of treatment, or within 90 days, with a notation of the outcome of the case.

All possible means should be used to make an epidemiologic study of each case with an effort to trace all sexual contacts and get all new cases under treatment.

the facilities of district and full-time county health officers and their nursing staffs will be available to assist the physician if he desires this service. He is urged to make full use of these facilities. **Prenatal blood tests for syphilis.** John Hall. Pub. Health News, Trenton, 24: 78-181, Dec. 1940.

Reports from approved laboratories show that at least 48,800 prenatal tests for syphilis were made in New Jersey in compliance with the prenatal examination law during the year beginning July 1, 1939. Slightly over 1 percent of the women tested showed positive results, which would indicate that about 600 of the 60,000 babies born each year have syphilis from their mothers.

Three months after tests are made a written letter is sent to the physician. In the next 6 months 483 such questionnaires were sent out, and 430 (89 percent) were answered. These replies showed that of 1,000 women who had been tested 34 percent had been tested before the fifth month of pregnancy, 55 percent from the fifth to the eighth month, and 11 percent at or near the birth of the baby. Only 24 percent of the women admitted knowing they had syphilis; 23 percent said they had had previous treatment; 70 percent had treatment after the prenatal tests.

The second questionnaire, inquiring about the baby's condition, is sent out a month or two after the time for the termination of the pregnancy. Facts from the replies concerning 124 babies whose mothers had positive blood tests are shown in a graph. Of the 84 mothers treated prior to the fifth month, 1.2 percent of the babies had syphilis, 6 percent died soon after birth, and 4.8 percent were stillborn. Of the 40 mothers without such treatment, 15 percent of the babies had syphilis, 7.5 percent died soon after birth, and 17.5 percent were stillborn. That is, the babies were normal in 88 percent of the first group, and in 60 percent of the second group.

Information is available from 88 of a group of 100 babies who were apparently healthy but had not had blood tests and were followed up by nurses. On 38 of

these babies blood tests were done; 2 were positive. Mothers and doctors promised tests later for 19 babies. Three babies died.

In 53 prenatal clinics in the State, 12,228 women had their blood tested in 1939, and of these only 2.2 percent gave positive results. Of the 5,744 babies born to these clinic cases only 24 (0.4 percent) were definitely diagnosed as syphilitic.

The number of cases of syphilis reported to the State health department in patients under 10 years of age, and especially under 1 year of age, is going down in spite of much larger numbers reported in almost any other age group.

1941 venereal disease control program in up-State New York to stress cooperation with national defense authorities. News Digest of the Milbank Fund. (Mimeographed) v. 7, no. 4, Dec. 1940.

The cooperative campaign for the control of syphilis, carried on by the State Charities Aid Association and the New York State Department of Health in up-State New York, will place special emphasis during the coming year on the following measures: (1) To stimulate provision of adequate facilities for the detection of syphilis and the provision of follow-up service among men called up for military training under the Selective Service Act and among their contacts and sources of infection; (2) to stimulate the local application of programs for the examination, treatment, and health education of the 30,000 men taking vocational courses in so-called "defense schools" to fit themselves for jobs in war industries; (3) to stimulate and assist those localities in and near which there are, or will be, large concentrations of troops to combat vice and other objectionable conditions favoring the spread of the venereal diseases to the troops as well as to the civilian population; (4) to promote the provision of service for men employed in war industries.

During the past 9 years this program, to which the Milbank Fund has contributed, through grants to the State Char-

ties Aid Association, has been given over to arousing, sustaining, and increasing citizen interest in the support of suitable programs for the control of venereal diseases.

North Carolina's anti-syphilitic program. Carl V. Reynolds. *Health Bull.*, Raleigh, 55: 7-10, Dec. 1940.

The North Carolina State Board of Health undertook making a serologic survey to determine the incidence of syphilis among the 448,555 young men who registered for the draft on October 16. The submission to these tests was purely voluntary. So many registrants took the test that before noon on registration day many of the counties had to be sent more tubes in which to submit samples of blood. Within a week after registration more than 100,000 blood samples had been sent to the State laboratory. In one county, 98.8 percent of the young men who registered presented themselves for examination; in another county, 92.66 percent. The effects of this survey will reach far beyond benefiting only those men who are drafted.

For several years this State has been engaged in a definite program looking toward the eradication of venereal diseases. During the biennium 1928-1930, there were only 8,542 cases of syphilis reported to the State board of health, and 119,860 Wassermann tests were run in the laboratory. When these figures are contrasted with those for the 4-year period 1936-1939, when 131,984 cases were reported and 1,014,229 serologic tests were made, the progress that has been made is seen to be striking. The number of treatments given in supervised clinics increased from 119,581 in 1936 to 814,825 in 1939.

In 1939 a survey made of 9,533 prisoners in 80 camps throughout the State showed that 2,229 individuals reacted positively to serologic tests, or 23.3 percent of the total prison population surveyed. Because of the enlightened public consciousness, the passage of a premarital

and of a prenatal examination law secured in 1939.

Commercialized prostitution and venereal-disease control. The results of suppression of commercialized prostitution on venereal disease in the city of Vancouver. Donald H. Williams. *Canad. Pub. Health J.*, Toronto, 31: 461-472, Oct. 1940.

The author states that professional prostitutes exploited illegally in commercialized prostitution in the city of Vancouver are highly infected with venereal disease. In that city commercial prostitution has been a prolific source of venereal infection. However, the effective enforcement of sections of the criminal code directed against commercial prostitution has reduced venereal disease in the male population of the city.

Prior to the institution of a policy of effective law enforcement, of 358 patients admitted to the Vancouver clinic suffering from gonorrhea, 88 (24.6 percent) named professional prostitutes illegally operating bawdyhouses as a source of their infections. The male clientele of the clinic consists largely of indigents, relief recipients, and a few from the lower-wage brackets. Among patients in a better financial position the incidence of infection from bawdyhouses would probably be higher.

From a median monthly level of 2 patients with venereal disease treated at the Vancouver clinic during a period of 13 months before suppression, the level dropped precipitously to 193.0 during a period of 15 months after suppression, a reduction of one-third. Before suppression, professional prostitution accounted for at least 24.6 percent of gonorrhea in men treated at the Vancouver clinic; after suppression, for only 12 percent.

It is the duty of the health department of Canada to create public consciousness of the menace of the bawdyhouse to public health, and to create a public demand for law enforcement which does not

harass in a superficial manner the
coited diseased women, but which
shes the madams and their cohorts
nd the scene with jail sentences and
vy fines. As long as the exploiters
make profits, so long will commer-
zed prostitution last in a community
so long will needless venereal disease
pread. Suppression of prostitution as
vided for by the criminal code of
ada and as approved by health au-
ities seeks not to wipe out prostitu-
but to make it inaccessible and re-
e it to a man-woman relationship free
n the mercenary participation in this
tationship of a third person.

the city of Vancouver a cooperative
t between health and law-enforce-
t departments has demonstrated the
adness of the policy of suppression of
mercialized prostitution. The public
th has been improved, an unsavory
merce has been reduced; and perhaps
example has been set for other
munities.

venereal-disease control in British Co-
mbia. Editorial. *Canad. Pub.*
Health J., Toronto, 31: 489, Oct. 1940.

he author comments on an article by
iams in this issue of the *Canad. Pub.*
Health J. (pp. 451-472) in which he dis-
es commercialized prostitution and
real disease control.

Toronto the police department has
many years pursued a policy of abso-
suppression of commercial prostitu-
Where such a policy is not the rule,
ously the prostitute will be the com-
est source of infection. The contacts
ne individual prostitute under such
umstances are many, and, as most
itutes are diseased, their clients be-
e diseased and the venereal disease
trises proportionately. Where a "red
" district is closed and the law is
tly enforced, the number of contacts
eases just as the customers of a store
spear if the owner closes its doors or
store burns down.

The presence of tolerated or legalized
prostitution in a community has other
disastrous effects. Moral standards are
lowered, and the total of irregular sex
relationships, aside from prostitution, in-
creases just as it decreases if severe
repressive legislation is instituted as a
result of the development of sound public
opinion.

To anyone who has studied the situa-
tion, arguments in favor of organized
prostitution as a means of controlling
venereal disease are utterly futile. The
highest venereal disease rates are invari-
ably found in those parts of the world
where prostitution is legalized and segre-
gated. When prostitution as a business
is successfully attacked, the first step has
been taken not only toward raising moral
standards and civic self-respect, but also
toward raising health standards.

Causes of blindness in Minnesota.

Charles E. Stanford. *Minnesota Med.*,
Minneapolis, 24: 1-3, Jan. 1941.

In a group applying for financial aid
as needy blind the factors responsible for
blindness have been studied to determine
how much blindness is possibly prevent-
able or remedial. There were 768 detailed
records available at the time this study
was made. Only cases considered eligible
for aid from a visual standpoint were
included. In the group of infectious
diseases there were 241 cases, among
which there were 2 cases of gonorrhea,
37 of ophthalmia neonatorum, 10 of pre-
natal syphilis, 47 of acquired syphilis, 27
with a clinical diagnosis of syphilis (84
cases of syphilis or 10.9 percent of the
total).

The majority of those blind from syph-
ilis are adults, affected in the 4th or 5th
decades. Early and adequate treatment
of primary syphilis could materially re-
duce this number. Routine Wassermann
tests on all expectant mothers, and
prompt institution of treatment of all
mothers with positive reactions would
reduce the number blind from congenital
syphilis.

The Biochemistry of the Gonococcus and Its Practical Importance

WOLFGANG A. CASPER, M. D.

THIS time when most medical and biomedical journals talk about a 90-per-cent-cure of gonorrhea by chemotherapeutic means so that the problem of gonococcal infection seems to be solved, any further comment on this subject seems superfluous. Even if these claims were verified, however, the remaining 10 per cent and the vast army of those still exposed to infection offer sufficient problems to justify further research on the biology of the gonococcus.

Recent advances in the chemotherapy of gonococcal infection have directed study to the mode of action of these therapeutic agents and have diverted attention from the much needed research on the biology of the gonococcus and the immunologic effect of this infectious agent on the human organism.

These seemingly theoretical considerations have practical significance. Without the aid of so-called specific immune reactions, for instance, sulfanilamide is said to be effective in only a small percentage of early cases.

And since vaccine therapy is postulated as the method of increasing these antibodies and accelerating their effectiveness, the failure of specific biologic therapy so far is sufficient proof of our lack of understanding of the basic facts concerning the gonococcus.

Although research in this direction has kept up with the progress made in other infectious diseases, recent work

from the Department of Urology, New York University College of Medicine, New York,

read at the Sixth Annual Session of the American Neisserian Medical Society, New York, N. Y., June 10, 1940.

in biochemistry is able to give us better insight into the biologic characteristics of the gonococcus and a deeper understanding of the pathogenesis of gonorrheal infection.

Experiments on the biochemistry of the gonococcus conducted by us for the first time in 1929 were patterned on investigations originally carried out on the antigen of the pneumococcus.

In order to make myself clear to the nonimmunologists, I shall briefly recapitulate the milestones of research on other bacteria. The conception of antigen involves two aspects, antibody production in vivo and specific reactivity in vitro. These properties have been considered inseparable and have been ascribed to the protein molecule. Avery and Heidelberger, in 1923, showed that the complex antigen of the pneumococcus can be split into two chemical substances. One of these is the chemical nucleus of the pneumococcus cell, resembling a nucleoprotein which was common to all representatives of the species, virulent as well as avirulent. In addition to this species-specific protein, they were able to isolate (but from virulent organisms only) a polysaccharide which was extremely specific, reacting only with the homologous antiserum. This substance was found to be chemically different for each of the types investigated.

According to Landsteiner's theory this type-specific carbohydrate was considered to be a "haptene," a substance reacting specifically in vitro but incapable by itself of engendering antibodies in vivo.

Schiemann and Casper in 1927, however, succeeded in producing immunity

and, indeed, type-specific protection in mice by injecting the protein-free polysaccharide fraction prepared by them. Our carbohydrate substance seemed to be a complete antigen. (Biologic proof by means of active immunization was even more sensitive than serologic reaction and showed the high potency of minute doses of these substances.) Our work was confirmed in 1931 by Wadsworth and Brown and subsequently led to a long series of investigations on the pneumococcus among which are the experiments of Francis and Tillet showing antibodies in humans by the use of specific carbohydrates for skin tests, and finally the attempt by Felton to protect a large series of CCC workers against pneumonia with such an antigen.

Analytic methods similar to those employed by us in determining the antigenic structure of the pneumococcus were applied to the gonococcus group in order to ascertain whether gonococci contain a carbohydrate fraction and the relationship between this carbohydrate and type-specificity, virulence, and toxicity.

For the pneumococcus an internationally accepted system of nomenclature has existed for some time, and the practical application of this fact can be seen in the different prognoses which it is possible to give in pneumonia based on various types. In the case of the gonococcus no such system existed, and we attempted to classify these organisms on the basis of comparative agglutination tests.

We found two main types. Type I, as shown by Torrey in the United States and by Tulloch in England, was present in the majority of cases while two other types played a minor role. Type-specific antiserum prepared from type II did not agglutinate type I, and vice versa.

From each of these serologically different types we succeeded in obtaining protein-free carbohydrate fractions which were shown to be responsible for the type-specific serologic reaction. In addition, we succeeded in isolating from both virulent and avirulent strains a protein which did not react with any of these

antisera and which displayed the characteristics.

The completely different chemical constitution of both types now supplies with a new concept of virulence and infectiousness in gonorrhea.

Let us now discuss the application of this new concept. As I stated before the type-specific carbohydrate can only be obtained from virulent strains. Accordingly, gonococci have to be freshly isolated from acute infections. We have no other means of assuring virulence *in vitro*. One culture, after it had been transplanted on artificial media for a year, showed a considerable decrease in the quantity of carbohydrate (which could be isolated) and, at the same time, lost its serologic specificity so that it now reacted with antisera from other gonococcus types. Similarly, gonococci cultured from chronic cases always show these overlapping reactions and cannot be classified in either of the five groups. Nor can one prepare any measurable amount of carbohydrate from such organisms. There is, apparently, a close relationship between the carbohydrate content and the virulence of gonococci.

Degenerative changes appear with aging of gonococci which, as I showed at the Third International Congress of Microbiology in 1939, affect not only their chemical constitution, but also their cultural and morphologic characteristics. The gonococcus, when newly isolated from acute infection and grown on special media, forms translucent colonies with papillae and dentate margins. On aging, these characteristics are lost and the colonies become whitish and smooth. Even the morphology of these organisms may change from diplococci to large single cells.

I might state here that between the extremes of Barbellion, who does not recognize any morphologic variants, and the gram-positive staphylococcus-like forms of Ash and Raven there are variations which one can prove to be gonococci. These changed forms can be reverted

in original characteristics. In the living tissues they are seen very rarely because it is extremely difficult to differentiate them from other bacteria, but they exist.

The practical value of these studies becomes evident in investigations such as one which I conducted with Studdiford and Scadron on chronic adnexal diseases in women. The conception of the American gynecologist is that chronic recurrent adnexitis does not serve as a focus of infection because gonococci die in closed body cavities. We were able, however, to cultivate gonococci (living under aerobic conditions) from tubes and ovaries showing no pathologic signs of inflammation in 60 percent of the operated cases, even as long as 10 years after the onset of the infection. Such a surgical focus, of course, remains a constant danger for further spread of infection. Some of these cultures showed the pathologic variations previously mentioned on their first transplants, but could revert later to characteristic diplococcus forms.

We know then that a correlation exists between degenerative changes in the gonococcus cell and the symptomless carrier state of the individual. Just as the gonococcus undergoes degenerative changes after transplantation from the infected individual to artificial media, as observed in colony formation and loss of type-specific reactivity, so, also, does the gonococcus by adaptation to the human host undergo a similar process by gradual changes in its chemical constitution.

Just as a degenerating strain may undergo reversion and regain its original morphology and type-specific serologic reactivity, so may the gonococcus in the living tissues under certain conditions, such as additional blood supply during menstruation, regain its type-specific carbohydrate and its virulence and thus explain the exacerbations in symptom-free carriers.

Observations on other bacterial pathogens support our opinion that an essential

relationship exists between carbohydrate content and the capacity of the organisms to produce disease.

Not only have the carbohydrates afforded us a better understanding of the pathogenesis of the disease, but they have proved to be of considerable diagnostic importance.

Biologic skin tests with the carbohydrate of the gonococcus, like those with the pneumococcus, are effective with minute doses— $8/1,000$ of a milligram of purified carbohydrate injected into the skin of infected individuals provided not only diagnostic skin reactions, detecting infection when bacteria could no longer be found, but also aided in determining the type of gonococcus responsible for the infection.

These findings have been confirmed by a number of authors in different parts of the world. In 1935 Mutermilch and Grimberg in France succeeded in preparing identical carbohydrates, and Barbellion and Feld, using Mutermilch's fraction, found the skin test almost 100 percent specific.

Pinetti in Italy confirmed the presence of the carbohydrate fraction in 1937. But his skin tests were less satisfactory due to the method of preparation and the use of avirulent unclassified strains.

On the other hand, the bacterial antigen is naturally much more complex in its chemical constitution than has been indicated. Boor and Miller, for instance, reported their isolation of a somatic carbohydrate from gonococci. The substance was protein-free, but closely related to the protein-free fractions of meningococci and *Micrococcus catarrhalis* and even to type III pneumococci. They explain the cross reactions with the pneumococcus antiserums. How much less can it be brought into accordance with our findings that even the carbohydrates of type I and type II gonococci did not show any serologic cross reaction and were even chemically different? As I pointed out previously, there may be a species-specific carbohydrate, like the one Rake and Scherp described in meningococci, since the gonococcus is a complex organism. Their

work, accordingly, as might seem from the paper read at the last meeting of this society at Milwaukee, does not disprove the existence of the type-specific carbohydrate.

The existence of a polysaccharide giving diagnostic skin reactions was again confirmed last year by Rossett. But he obtained the carbohydrate fraction from gonococcus toxic bouillon filtrates in the form of Corbus-Ferry filtrate.

So-called toxic filtrates have been rejected for therapeutic purposes. If it were possible to produce antitoxic antibodies, it would be much more advisable (as Herrold suggested in 1925) to supply the infected individual with such an antitoxin. Herrold, indeed, did obtain toxic skin reactions (as manifested by a blanching phenomenon) with such filtrates. Corbus, on the other hand, states that he produced allergic skin reactions with his toxic filtrates. Specific allergic reactions cannot be expected, however, if one is dealing with an ectotoxin in the sense Ferry wants it understood.

There can be no doubt that the substance with which Rossett is dealing is the polysaccharide fraction and that the skin reactions produced with this substance in gonorrheal infections are due to this carbohydrate fraction. He did prepare it from a bouillon filtrate, but it was not the toxic Corbus-Ferry principle.

As our knowledge progresses we should, therefore, be careful not to use any more biologically undefined or chemically unrefined material for diagnosis or therapy.

The recognition of the complex chemical structure of the gonococcus now supplies us with an explanation of the unsatisfactory results obtained in diagnostic skin tests with whole bacteria, commercial vaccines, or filtrates and shows that with these procedures we were only using *non-specific proteins*.

It is the *protein* in the complex bacterial cell which contains the toxic component of the gonococcus antigen and which is largely responsible for the non-specific serologic and biologic reactions.

As little as 8/10,000 of a milligram the purified protein can elicit skin reactions in normal individuals. It would appear that the biologic test is much more delicate for the detection of protein than our chemical tests, since any minute amount of protein still adherent to the carbohydrate would manifest itself in the control skin test. The chemical separation and the production of the specific effective principle is not easy, but it presents the gist of the whole problem.

Thus, it is seen that it is of more than theoretical interest to the bacteriologist that the gain or loss of this carbohydrate portion in the complex structure of the gonococcus cell has a vital influence upon degenerative changes in colony formation, loss of serologic classifiability, and even changes in morphology of the diplococcus. By adaptation of the gonococcus to human tissues the same mechanism may explain the pathogenesis of the symptomless carrier state and the mystery of the repeated flareups without reinfection.

In summary, the study of the biologic and chemical characteristics, with particular emphasis on the antigenic capacities of the type-specific carbohydrate has given us a definite type-specific diagnostic test in gonococcal infections. With the knowledge of the part the protein plays in skin testing, it has explained why all our former efforts at specific diagnosis had to fail. With the aid of the carbohydrate fraction, correlations could be made by skin testing between skin reactivity, the clinical status of the patient and his response to therapy. This test is especially valuable in symptomless carrier cases when even the culture method deserts us. As this test serves to determine the type with which the patient is infected, it gives us a constant antigen for serologic testing. The introduction of an internationally recognized classification would be an aid in epidemiologic studies.

In order to determine definitely whether this fraction has the *antigenic capacity to render protection*, large series

periments similar to those which have been done with pneumococci have to be instituted. Where pneumonia will strike, we can hardly foresee. But we could control potential gonorrheal infections in view of their predominance in groups of low social standing.

Gonococcal infection is not a solved problem, even with the new therapeutic discoveries. It is the therapy-refractory case, the number of which is larger than anticipated, and the symptom-free carrier which remain a public health problem. Just as we could not treat malaria, in spite of our knowledge of quinine, if we did not know the life-cycle of the parasite, so do we need extensive studies of the antigenic structure of the gonococcus and its effect on the human organism to give us a thorough knowledge of gonococcal infection and lead the way towards its prevention.

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The Effect of Sodium Thiosulfate on Excretion of Arsenic

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SINCE ITS introduction in 1920 as an antidote for arsenical poisoning, sodium thiosulfate has been subjected to numer-

ous investigations to determine its pharmacologic action and therapeutic efficacy. Even after a score of years a controversy still exists in regard to its action. A moderate amount of experimental work has been conducted and yet, surprisingly enough, not as much as one would expect considering the importance of the problem and universal use of this

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We wish to express our appreciation to Dr. J. H. Watkins, Statistician, Division of Venereal Diseases, U. S. Public Health Service, for his assistance in preparing this manuscript.

compound. The rationale for its clinical use has been based primarily on the premise that it will mobilize arsenic stored in the tissues and organs of the body and facilitate its excretion. For the most part the experimental studies have been designed to verify this supposition. Cannon (1), Kuhn and Reese (2), Groehl and Myers (3), Ayers and Anderson (4) all felt that they satisfactorily demonstrated that administration of sodium thiosulfate increased the arsenic content of urine in man and the experimental animal. On the other hand, studies conducted by Young (5), Oppenheim and Fantl (6), and Mattice and Weisman (7) led them to believe that sodium thiosulfate did not appreciably increase arsenic excretion in the urine.

Further expression of the dilemma can be found in certain textbooks on syphilology (8) and pharmacology (9). One authority (8) is inclined to ascribe the disparity between laboratory data to the faults and difficulties entailed in the technic of arsenic analysis. In addition to this fact, it occurred to us that another shortcoming of the few reports where human subjects were used for study was that the material was not as appropriate as it might have been. That is, the test cases cited were equivocally those of arsenic poisoning, and the extent, source, and interval of time since last exposure were not specified. We believe that this type of case is not the best material to prove the issue, as minimal quantities of arsenic are difficult to evaluate and may be normal values. Furthermore, it has been demonstrated by Voegtlin (10) and Bulmer (11), and many others that the major avenue of excretion of arsenic from the body is the bile and, therefore, the intestinal tract. The work of Appel and Jankelson (12) suggested that the main effect of sodium thiosulfate was its cholegic action, that it accelerated the excretion from the main storage depot, the liver. Owing to these criticisms, we felt that a reappraisal was indicated, and a more reasonable approach to this entire problem would be to select persons who were known to have large amounts of

arsenic in their tissues and to determine the arsenic content of their total excretions, both that which occurs in the stool and urine, by a technic of analysis of arsenic which has been scrupulously controlled.

METHOD

It was our experience after perusal of the literature and attempts to use several different methods of arsenic analysis that considerable difficulty was entailed in the analysis of arsenic, particularly in biologic material. There are numerous reports on this particular question (13, 14, 15). A comprehensive review made by Heller (16) in 1934 discusses a variety of methods. Some workers in previous studies have made little comment regarding the establishment of the validity of the method which was utilized. The most recent work was done with the electrolytic Gutzeit apparatus. However, we were able to recover only a partial percentage of a known quantity added to both urine and stool by use of this apparatus even after diligent and extensive trial.

We then turned to a method outlined by Allcroft and Green (14) which also failed to satisfy our demands for recovery of a reasonable major portion of a test substance. We abandoned these and resorted to the old, unmodified Gutzeit method as outlined in the "Methods of Analysis" of the Association of Official Agricultural Chemists. This method satisfied our clinical requirements of maximum recovery in our test substance. Moreover, it has the advantage that large volumes of material can be analyzed with facility at one time. Of course, the admonition to use arsenic-free reagents such as zinc shot, sulfuric and nitric acids must be strictly observed, and standards must be run simultaneously with each group of unknowns. To establish the validity and consistency of this method, samples of urine and feces were analyzed which contained from 0.15 to 1.4 per cent added arsenic in the form of arsenic trioxide. The mean recovery was 98.9 per cent and the standard deviation, 9.5 per

ent. Fifteen samples of feces similarly treated showed a mean recovery of 100.1 percent and a standard deviation of 15.0 percent. These showed that 71 percent of feces analyses and 50 percent of urine analyses would be exact to within a percentage error of 10, which appeared satisfactory for a clinical study of this type.¹

METHOD OF DIGESTION OF MATERIAL

Urine.—Into a 300-ml. Kjeldahl digestion flask is measured a convenient aliquot (50 ml.) of the 24-hour urine specimen, 15 ml. of arsenic-free sulfuric acid, 15 ml. arsenic-free nitric acid, and 1 ml. of 10 percent copper sulfate. A couple of glass beads are added to prevent bumping. The mixture is boiled over a gas flame for at least $3\frac{1}{4}$ hours.

Feces.—For examination of feces, however, the following routine was used: The feces are dissolved in 15 percent sulfuric acid to make a homogeneous solution of roughly 10 to 20 percent by weight of the feces. A convenient aliquot of this solution (40 ml.) is placed in a 300-ml. Kjeldahl digestion flask with 15 ml. of arsenic-free sulfuric acid, 25 ml. of arsenic-free nitric acid, 1 ml. of 10 percent copper sulfate and a couple of glass beads. This is heated vigorously for $7\frac{1}{4}$ hours with some nitric acid added from a dropping bottle as charring occurs. Usually the digest is colorless at the conclusion of this period of heating. If not, heating should be prolonged. When the digest is colorless, it is diluted to about 50 ml. with distilled water, and hydrogen sulfide is used as a precipitating agent to remove nitrous oxide fumes. This requires about 2 to 3 minutes. Then further boiling is applied for about $3\frac{1}{4}$ hours.

REDUCTION AND MEASUREMENT

Digests are diluted to exactly 100 ml. and duplicates of 40 ml. each are meas-

ured out into convenient glass bottles. (If 40 ml. amounts contain too much arsenic to measure by this method, fractions: i. e., 5 ml. or 10 ml. each, may be used and the volume made up to 40 ml. with 15 percent sulfuric acid containing 1 percent copper sulfate.) Standards of 1, 4, 6, 8, 12, and 24 gammas of arsenic are prepared from a solution of arsenic trioxide, preserving a concentration of 15 percent sulfuric acid and a trace of copper sulfate as in the digest. Then to each bottle, unknowns and standards, is added 5 ml. of freshly prepared 15 percent potassium iodide followed by 4 drops of 40 percent stannous chloride. These are allowed to stand for 15 minutes to insure reduction. Ten pieces of zinc shot, roughly spherical in shape, are added. After this, the regular procedure for the staining of sensitized paper by arsine is followed. The length of stain on both sides of the paper is measured and compared with the graph which has been plotted from the standards that have been run simultaneously, and the total amount of arsenic present is calculated.

We elaborate on these detailed instructions for digestion of the materials because we learned, after more than a year of repeated trials, that they were significant in producing maximum efficiency in analyses.

STUDY MATERIAL AND RESULTS

The material consisted of 24-hour collections of urine and feces from syphilitic patients following the completion of a course of neoarsphenamine, i. e., eight injections of 0.6 gm. each at weekly intervals. In all, 10 patients were studied, 6 of whom, after 4 to 6 daily analyses of feces and urine, were given intravenously 1 gram of sodium thiosulfate in 10 cc. of distilled water for 4 consecutive days, the urine and feces being concurrently analyzed for arsenic. The time between completion of the course and commencement of the collection of samples varied among the patients from 2 to 13 days. A control group of four persons receiving identical arsenical treatment were ex-

¹ The mean recovery in 29 samples of urine was 98.9 percent and the standard deviation, 5 percent. Corresponding figures for 15 samples of feces were 100.1 and 15.0, respectively.

amined for a corresponding period of time but were given no injections of sodium thiosulfate. The detailed analyses of the output of feces and urine for the two groups are shown in tables 1 and 2.

For presentation the findings have been combined into two curves (chart 1), the first showing the mean results of daily analyses in the absence of sodium thiosulfate, the second showing the mean daily arsenical output during periods of

TABLE 1.—Daily output of milligrams of arsenic recovered in urine and in feces of four syphilitics, following a course of neoarsphenamine. No thiosulfate given

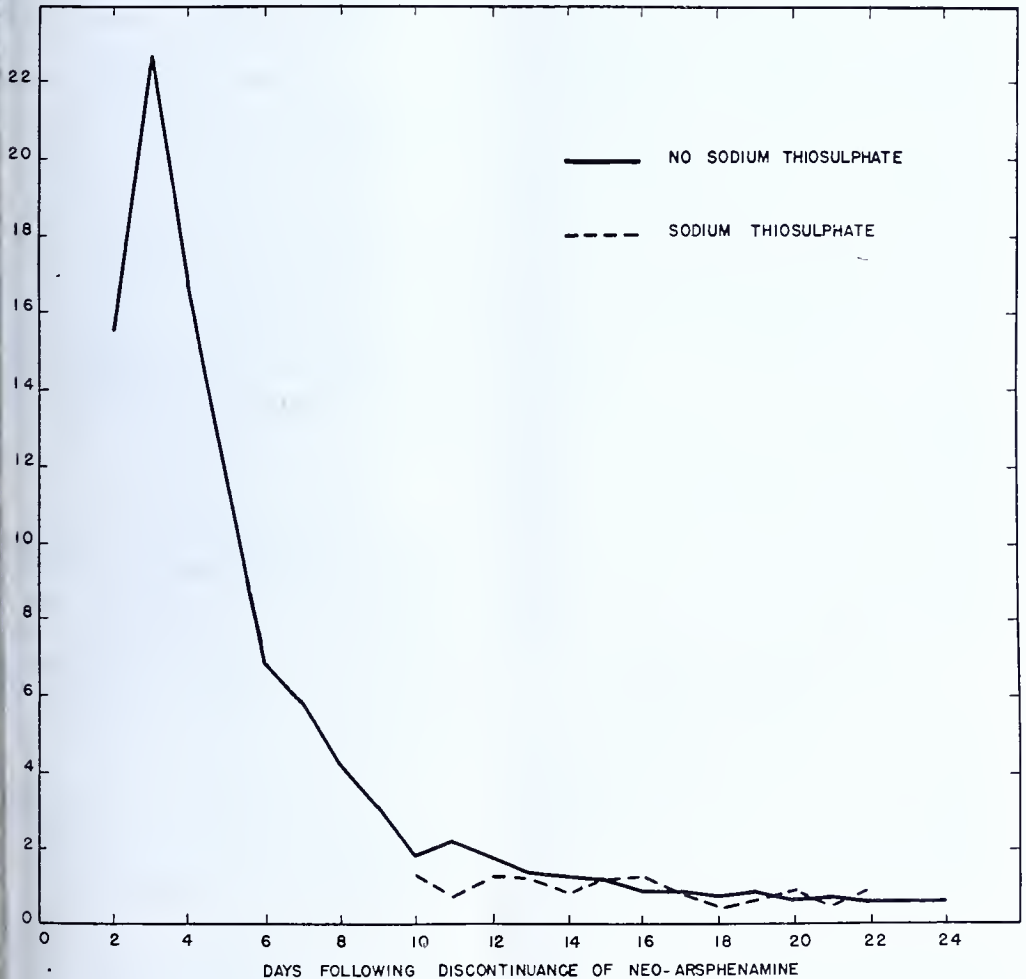
Days following discontinuance of course of neoarsphenamine	Case H. B. B.			Case B. B. C.			Case J. F.			Case C. H. K.		
	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
1												
2				10.56	4.92	15.48						
3				5.70	17.00	22.70						
4				4.00	12.80	16.80						
5												
6	2.64	3.55	6.19				2.49	0	2.49			
7	1.96	2.28	4.24	1.45	4.55	6.00	3.11	6.50	9.61			
8	1.32	1.38	2.70	1.31	1.82	3.13	3.45	5.50	8.95			
9	1.30	.74	2.04	1.15	1.40	2.55	3.00	5.55	8.55			
10	1.66	.66	2.32	.94	.90	1.84	1.42	0	1.42			
11	.98	1.09	2.07	.95	.53	1.48	.93	2.50	3.43			
12	1.03	.76	1.79				.87	1.80	2.67	.49	.53	1.02
13	.74	.71	1.45				1.18	.55	1.73	.65	.34	.99
14	.69	.64	1.33	.67	1.24	1.91	.53	0	.53	.36	.37	.73
15	.83	.68	1.51	.60	.75	1.35	.52	.85	1.37	.34	.38	.72
16	.78	.52	1.30	.59	.35	.94	.51	0	.51	.37	.26	.63
17	.33	.36	.69	.49	.19	.68	.38	.88	1.26	.63	.21	.84
18	.61	.14	.75	.53	.34	.87	.31	0	.31			
19	.60	.49	1.09				.39	.17	.56	.39	.22	.61
20	.46	.49	.95				.14	0	.14	.39	.16	.55
21	.47	.48	.95	.61	.14	.75	.40	0	.40	.25	.17	.42
22	.38	.36	.74	.37	.07	.44	.30	.15	.45	.28	.17	.45
23	.36	.24	.60	.37	.34	.71	.19	0	.19	.28	.22	.50
24	.45	.24	.69	.40	.08	.48	.27	.12	.39	.32	.14	.46

TABLE 2.—Daily output of milligrams of arsenic recovered in urine and in feces of six syphilitics following a course of neoarsphenamine. Data below the lines in each column are the amounts recovered during daily injections of thiosulfate.

Days following discontinuance of neoarsphenamine	Case N. C.			Case B. B. C.			Case J. L. C.			Case A. J.			Case J. H. L.			Case H. W.		
	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
6	1.14	10.75	11.89															
7	.70	4.80	5.50	2.00	1.84	3.84												
8	.29	4.25	4.54	1.00	2.75	3.75												
9	.45	1.28	1.73	.88	1.20	2.08				1.92	1.31	3.23	.75	1.39	2.14			
10	.23	.95	1.18	.56	1.25	1.81				.85	1.11	1.96	.63	.73	1.36			
11	.22	.44	.66							.88	1.28	2.16	.82	.62	1.44			
12	.31	.42	.73							.66	.79	1.45	.43	.78	1.21			
13	.27	.60	.87	.58	.12	.70	.45	.77	1.22	.82	.64	1.46	.81	.84	1.65	.48	.21	.69
14				.41	.19	.60	.42	1.04	1.46	.56	.18	.74	.54	1.10	1.64	.54	.89	1.43
15				.43	.71	1.14	.54	.32	.86	.55	.34	.89	.59	.41	1.00	.33	.24	.57
16							.26	.37	.63	.53	.71	1.24	.65	.53	1.18	.41	.52	.93
17							.50	.30	.80	.37	.32	.69				.42	0	.42
18							.31	.08	.39							.52	.24	.76
19							.37	.21	.58							.47	.12	.59
20							.44	.28	.72							.48	.46	.94
21																.31	.12	.43
22																.51	.28	.79
23																		
24																		

CHART I

THE EFFECT OF SODIUM THIOSULPHATE ON ARSENICAL RELEASE IN LUEPIC PATIENTS
FOLLOWING A COURSE OF EIGHT INJECTIONS OF NEO-ARSPHENAMINE



jection of sodium thiosulfate. The
st curve, primarily based on results for
e four control subjects, also includes
e preliminary analyses made on the
x subjects receiving sodium thiosulfate.
he latter observations were added to
prove the smoothness of the control
urve; their omission would change it in
o essential characteristic. That these
urves fail to differ markedly is corrobo-
ted by statistical tests of significance,
nd the fact is clearly established that
e release of arsenic is not affected by
ministrations of sodium thiosulfate
er the time periods used by us.

DISCUSSION

It is generally stated that following the administration of such a quantity of arsenic the body excretes it gradually over a period of several weeks. We found that the maximum excretion occurred within the first 9 days; thereafter the quantity of excretion fell rapidly to a level between 0.5 and 1.0 mg. daily, which was maintained for the duration of our experiment. Even after 24 days, the longest period any one of our subjects was observed, abnormally excessive quantities of arsenic were present in the urine

and stools, indicating that there was still considerable retention in the body depots. When the excretion of arsenic either in the urine or feces alone or in both combined is compared with the control subjects, it is apparent that there is no significant acceleration or increase following sodium thiosulfate administration. In individual instances, of course, there were slight increases or decreases over previous days, but we feel that they were not significant but that they only indicate fluctuations in normal noninfluenced excretion. Quantities of urine and stool varied in these subjects from day to day, sometimes quite definitely. Our data revealed that the content of arsenic was usually proportional to the quantity of material, which was true of test subjects as well as the control group. At no time did sodium thiosulfate produce any marked increase in arsenic excretion, as it should do if it were to be considered of clinical significance.

As has been said above, the normal curve of excretion is gradually diminishing from day to day, and to entertain the concept that diminished excretion of arsenic after daily administration of sodium thiosulfate is evidence of immobilization or retention of arsenic, would be quite fallacious.

The *modus operandi* of sodium thiosulfate therapy in arsenic poisoning has been suggested by numerous workers to occur in several ways (17, 18, 19, 20, 21). The strongest case for its clinical use has been the supposition that it accelerated arsenic excretion and depleted arsenic storage in the organism. It has even been a somewhat common practice to administer sodium thiosulfate to individuals suspected of having arsenic poisoning and to analyze quantitatively the urine for arsenic content before and after the administration of this drug. In cases in which the excretion of arsenic seemed to have increased, this etiologic diagnosis appeared to be supported. Cognizance should be taken of the fact, however, that a measurable amount of arsenic is excreted by normal individuals in fluctu-

ating amounts, dependent on such factors as diet, use of tobacco and cosmetics (22).

This study reveals that sodium thiosulfate does not mobilize, and probably does not immobilize, arsenic stored in body tissues. The inclusion of analyses of feces for arsenic content was purposely made in this study to assess the cholegog theories. But for all clinical purposes, appears that analysis of the urine alone is a sufficient criterion to determine abnormal arsenic excretion except within the first week after a massive dose of the material, when the main route for excretion is by way of the bile or intestinal tract. After this time the arsenic content of urine and feces roughly parallel each other.

SUMMARY

1. The pharmacologic action of sodium thiosulfate in the treatment of arsenic poisoning is still a controversial issue. A disparity exists in the results of previous studies in this problem, which might be explained on technical difficulties of arsenic analysis and the selection of subjects.

2. Ten syphilitic patients, each of whom had completed an orthodox course of neoarsphenamine therapy, were selected for this study. Six of them received sodium thiosulfate, while the remaining four were used as controls. The arsenic content of urine and feces was analyzed in these subjects over a period ranging from the first to the twenty-third day following the completion of the course of neoarsphenamine therapy.

3. The urinary, fecal, or total arsenic excretion was not significantly affected by administration of sodium thiosulfate in popularly used therapeutic dosage.

4. The question as to clinical efficacy of this compound in the treatment of arsenic poisoning might be raised, as the strongest case for its clinical use has been based on the supposition that it mobilizes the excessive arsenic stored in the body depots.

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DIAGNOSIS

Systolic gallop rhythm as a sign of aneurysm of the left ventricle. Report of a case. George V. LeRoy and Ralph C. Roberts. Am. Heart J., St. Louis, 21: 115-119, Jan. 1941.

Systolic gallop rhythms, when the extra sound is loudest at the apex, are generally thought to be of no clinical significance. In the case here reported, a careful search for the cause of systolic gallop rhythm led to the discovery of an aneurysm of the left ventricle and suggested that such an aneurysm, by distorting the mitral valve during systole, may cause gallop rhythm. In this case at least, the systolic gallop rhythm at the apex was certainly a sign of a pathologic process, namely, aneurysm of the left ventricle.

The patient, a 52-year-old Negro, was first seen in May 1938 when he was referred for an opinion as to arsenical treatment for his latent syphilis. He

had had a urethral chancre in 1918. He received antisypilitic treatment for 2 months in 1934. Early neurosyphilis was then diagnosed, and he was sent to a State hospital where he received 16 fever treatments and 16 injections each of bismuth and mercury compounds and neoarsphenamine. In February 1938 he was advised to resume treatment. On examination of the heart the sounds at the apex attracted attention. Electrocardiograms were interpreted as showing normal mechanism, with infrequent extrasystoles of supraventricular origin. Many other studies were then made to ascertain the cause of the systolic gallop rhythm. Fluoroscopic examination of the heart disclosed a small aneurysm of the lateral wall of the left ventricle, with characteristic out-pouching during ventricular systole. Simultaneous stethographic and electrocardiographic records confirmed the impression that the gallop sound occurred between the first and second heart sounds. The idea that a deformity of the mitral valve, with a sudden reflux of blood into the left auricle, may cause gallop, the authors feel, is supported by the direct and circumstantial evidence gained from their studies in this case.

The spinal fluid in Erb's syphilitic spinal spastic paraplegia. Erwin E. Peters. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 72-76, Jan. 1941.

The author presents the blood and cerebrospinal fluid serologic findings in 30 cases of Erb's syphilitic spinal spastic paraplegia. The blood serologic test was positive in 22 (73.3 percent) and negative in 8 (26.7 percent). The cerebrospinal fluid was not examined in 1 case. In 7 cases (23.3 percent) the fluid was normal; 4 other patients (13.3 percent) showed pleocytosis, protein increase, or abnormal colloidal curve, alone or in combination, but with Wassermann tests negative. In 11 cases (36.6 percent) the spinal fluid was either normal or the changes were nonspecific. Of 18 patients with positive Wassermann spinal fluid tests, the changes were moderate (Group II by

Moore's classification) in 6 (20 percent), maximal (Group III, the parietic formula) in 11 (36.6 percent), and unclassified in 1.

In 2 patients only were both blood and spinal fluid completely normal at the time of the examination, and both of these had a history of syphilitic infection with previous treatment.

The ratio of males to females was 5:1 of whites to Negroes, 2.5:1. In only 8 of 24 patients with information as to the date of infection had the onset of symptoms occurred within 6 years after the initial lesion, in 5 within 6 to 10 years, and in 11 within 10 to 37 years. Seventy percent of the group were 30 years of age or older at the time of the diagnosis.

Five patients (16.6 percent) improved clinically after antisypilitic treatment. This response was slight in four patients and marked in only one. Of the 30 patients, 83.4 percent remained stationary or became worse in spite of treatment. All of the patients who had repeated lumbar punctures showed serologic improvement in the spinal fluid, but there was no correlation between this and the clinical course. The author states that the most to be hoped for from treatment is the arrest of progress of the clinical picture.

Chronic tonsillitis in secondary syphilis—differential diagnosis from diphtheria and Vincent's infection. A report of 23 cases. Evan W. Thomas and David H. Goldstein. *New York State J. Med.* New York, 41: 256-259, Feb. 1, 1941.

That secondary tonsillitis is indistinguishable at times from diphtheria and Vincent's infection is not always appreciated by the medical profession. Of 23 cases of severe chronic syphilitic tonsillitis, 20 had been misdiagnosed by private physicians or clinics prior to their admission to the syphilis wards of Bellevue Hospital. Four patients had attended nose and throat clinics, 4 had been seen by private physicians, and 3 had been seen by consultants. There were 15 instances of membranous tonsillitis and 8 of the ulcerative or follicular type. The duration of symptoms had varied from

less than 2 weeks to over 3 months. Six patients had had positive tests for diphtheria and 1 had had a tonsillectomy, which did not cure the sore throat. In one of the 20 cases was syphilis regarded as the fundamental cause of the throat infection. By the time the diagnosis of secondary syphilis was established all but 1 of the 23 patients had a skin rash. Actual chancres were observed in only 3 patients. In every case, however, the history, the rapid healing of the throat following one injection of antarsenical, and the positive blood Wassermann reaction established the diagnosis. In the majority of cases Vincent's angina was the original presumptive diagnosis, but only 2 were reported as having had a positive smear before admission to Bellevue.

The diagnosis of syphilitic tonsillitis in most cases seems easy in retrospect, but there is nothing characteristic about the sore throats of secondary syphilis. Even the presence of a rash may not suggest syphilis. The authors urge that every patient with a chronic tonsillitis be given a Wassermann test and a thorough examination for stigmas of secondary syphilis.

Syphilis and diabetes mellitus. A critical study of their relation to each other in 1,000 cases of diabetes mellitus. John R. Williams. New York State J. Med., New York, 41: 252-255, Feb. 1, 1941.

The author analysed 1,000 clearly established standardized cases of diabetes mellitus from the Strong Memorial Hospital in his study of the significance of syphilis in such cases. Each one of the patients was examined clinically for syphilis and had one or more blood Wassermann tests made. There were 17 cases which showed positive clinical evidence of syphilis and positive serologic tests, and these cases were treated. This gives a ratio which is in accord with the experience of other observers and conforms to the incidence of the disease in the general population.

Patients with severe diabetes, that is say, those with low carbohydrate tol-

erance requiring large doses of insulin and whose metabolism is difficult to adjust, frequently show subpositive Wassermann reactions with one or more antigens. In this series there were 23 such cases. Antisyphilitic treatment for these serves no useful purpose and is usually upsetting. To determine the significance of the Wassermann test, a study was made of the records of the Strong Memorial Hospital. From 1926 to 1936, 312 patients were found who gave a 4-plus blood test on one or more occasions. None of these patients presented any historical or physical evidence of syphilis. None of the 14 cases in this group who came to autopsy presented any anatomic evidence of syphilis; some may have had syphilis at some time.

There was found no causal relationship between syphilis and diabetes mellitus. The rarity of syphilitic pancreatitis, excluding congenital syphilis, is shown by the fact that in approximately 4,800 necropsies not a single case was found.

The treatment of active or latent syphilis has little or no effect on the metabolism of diabetes mellitus.

A short contribution to syphilis of the thyroid gland. B. Polony. Dermat. Wehnschr., Berlin, 111: 966, Nov. 9, 1940.

The author reports the case of a 37-year-old woman who had been treated with X-ray and who had had an operation on the thyroid. In spite of this a fistulous process persisted in the neck region. The Wassermann reaction was strongly positive. A diagnosis of gumma was made. There was prompt healing under antisyphilitic treatment.

Carcinomatous metastases of the vulva resembling syphilitic papules. Case report. A. Winkelströter. Dermat. Wehnschr., Berlin, 111: 814-816, Sept. 21, 1940.

In June 1938 a 45-year-old woman was advised by her consort to see a physician because of small pimples on the genitalia.

She delayed going to a physician until October, at which time she complained of hemorrhoids. In February 1939 she had a severe hemorrhage from the anus for which she saw a gynecologist who referred her to the author because he suspected syphilis. Examination showed pinhead sized papules on the left border of the tongue, leukoplakia of the buccal mucous membrane, marked edema of the right labia with 6 to 8 cherry sized, round and annular, rose colored to red, indurated papules which extended as far as the anus. At the lower border of the right labia there was an ulcerated lesion with raised, irregular border. Partially ulcerated nodules could also be seen to extend from the anus outward. Nodules could be palpated in the rectum to a depth of 7 cm. The dark-field examination, the Wassermann, Kahn, and Meinicke tests were negative. Biopsy showed the lesions to be adenocarcinoma.

Early diagnosis of granuloma inguinale.

Robert Brandt and T. Schley Gatewood. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 48-55, Jan. 1941.

According to the authors, the favorable effect of antimony preparations in cases of granuloma inguinale diminishes in proportion to the duration of the disease. An early diagnosis is necessary for successful treatment and, in most cases, it can easily be obtained by the evidence of Donovan's bodies. Certain clinical signs will suggest the desirability of this examination or indicate the necessity for its continuation in spite of a few negative smears. The lesions of this disease are elevated from the very beginning but not ulcerated. This fact provides for differentiation from superficial inflammations (e. g. balanitis) or chancroid. The bright red velvety surface which easily bleeds, and the soft structure of the granulations form a contrast to the lesions of primary and secondary syphilis. The absence of buboes is important. The characteristic buttonlike granulation may represent a primary lesion as well as a form of

propagation in cases of long duration. There may be a considerable resemblance to hypertrophic syphilitic papules. The syphilitic papules, however, are covered with epidermis and hence are dry at the onset, whitish grey in case of maceration, never bright red and velvety. They develop and change rapidly in appearance. Granuloma inguinale is slow in development, with rare signs of healing or scar formation or, in early cases, of ulceration. This makes the surface homogeneous. Positive blood Wassermann reactions and skin tests for venereal lymphogranuloma or chancroid do not, of course, rule out granuloma inguinale, but biopsy permits a definite diagnosis.

The authors present five case reports of patients with the disease.

Pulmonary case reports. Robert A. Peers. *Pacific Coast Med.*, San Francisco, 8: 17, Jan. 1941.

The author reports the case of a young woman who was referred to him for supposed allergic asthma, with a questionable complicating tuberculosis. She did not react to tuberculin either intracutaneously or subcutaneously, and the sputum was repeatedly negative for tubercle bacilli. Nevertheless, a roentgenogram showed marked exudative infiltration of both lungs similar to tuberculosis. She was given antisyphilitic treatment with heavy metals and potassium iodide. Roentgenograms taken 2 months and 4 months following the beginning of treatment showed gradual and then final clearing of the patches of exudation which were seen in the first picture.

A man 57 years of age was referred with a history of asthma for the previous 2 years. A roentgenogram showed marked exudation in both lungs, but, in spite of the fact that large quantities of sputum were raised daily no tubercle bacilli could be found, although many specimens were examined. Two Wassermann tests of the patient were slightly positive. Treatment by arsphenamin caused complete clearing of the pulmonary

ary condition. Now, 13 years later, the patient is in good health at 70 years of age.

Congenital syphilis in only one of twins.

Frank R. Smith, Jr., and John M. Spence, Jr. South. M. J., Birmingham, 34: 147-152, Feb. 1941.

The concept of the occurrence of congenital syphilis in only one of twins has been presented from time to time in the literature. The older case reports, before the development of serologic tests and before adequate pediatric follow-up was considered necessary, were largely philosophical dissertations and are of no value. More recent critical observers, however, have contributed a series of 12 individual case reports of this phenomenon. The authors tabulate the relevant data of these 12 cases, and present the reports of 5 cases in detail. Their own experience is based upon two personally observed cases of syphilis in one of newborn twins and other cases which were found in a search of the records of the Johns Hopkins Hospital. Since 4 of these occurred in the course of 44 twin pregnancies to 40 women with syphilis, the condition is not rare.

The criteria which must be fulfilled before the diagnosis of congenital syphilis in only one of twins may be made are as follows: (1) The congenital nature of the infection in the syphilitic twin must be clearly proved. (2) The fact must be established beyond peradventure that the apparently nonsyphilitic twin either has had syphilis in the past nor is in the process of developing it.

The first of these requirements is easily satisfied in the newborn infant, but becomes more difficult in the older child. It is possible in the adult only when classical stigmata of the congenital infection are present. In the absence of such stigmata, the possibility of syphilis acquired in childhood must be considered.

The situation is similar in considering the apparently nonsyphilitic twin. If the infant is seen shortly after birth, adequate follow-up is necessary to establish that he is not developing syphilis. If he

is first seen in later life there is always the possibility (though remote) of congenital infection with spontaneous cure before the examinations were conducted.

All of these cases were of double ovum twins. Many theories have been advanced to explain the phenomenon of congenital syphilis in only one of dizygotic twins, but none is completely in keeping with the observed facts. The operation of sheer chance probably provides the best explanation. The fetus of a woman with syphilis, it is thought, becomes infected in utero by the transplacental transmission of the infecting organism from the maternal-fetal circulation. There is good evidence that this transmission depends on the development of syphilitic inflammation in the placenta, so strategically placed that, as it extends, it breaks through the normal barrier between the fetal and the maternal circulations, with consequent escape of the spirochetes into the former. Regardless of other controlling factors, in many cases chance alone seems to determine whether this does or does not occur during the pregnancies of many women with syphilis. Such women may give birth to a succession of normal and syphilitic children arranged in any sequence.

Syphilis. C. Guy Lane and G. Marshall Crawford. New England J. Med., Boston, 224: 110-116, Jan. 16, 1941.

The authors discuss the medical progress made against syphilis during the past year and briefly review certain important articles which have appeared in the literature on syphilis during this period. They discuss the subject as follows:

1. Public health: The role of the private practitioner in controlling syphilis as discussed by Stokes. Syphilis in industry as reported by Russell and by Wilzbach. Illegal and unethical sales of venereal disease "remedies" by pharmacists as reported by Edwards and Kinsie. Follow-up studies of patients with early syphilis from the prearsphenamine era reported by Wilners.

Venereal disease control in the Navy as reported in the annual report of the Surgeon General of the United States Navy for 1938.

2. Immunity: A study by Turner, who found that syphilitic rabbits develop humoral antibodies to syphilis during the course of their infection. Kemp's review of immunity in syphilis.

3. Serology: The continued work of the Committee on the Evaluation of Serodiagnostic Tests for Syphilis. Brenner's report on results of the Davies-Hinton test of the cerebrospinal fluid. Mohr and Smith's study of the supposed daily variations of the reagin content of syphilitic serum (they concluded that quantitative flocculation technics are valuable in eliminating false positive reactions in questionable cases). Ingraham and Mayer's investigation of the menstrual cycle on the blood serologic test for syphilis. Greene and his associates' report of a quantitative study of syphilitic serum with Hinton and Kline tests, giving information indicating reagin titers and eliminating zone reactions. Kahn's description of a newly developed serologic verification test, which is a modification of the standard Kahn technic. Erickson and Eagle's comparison of the spirochete complement fixation reaction with the Eagle flocculation and Wassermann procedures. Clifton and Heinz' report of the finding of 82 children with false positive or doubtful serologic reactions out of 5,620 new patients examined in one year's time at a children's hospital. Moore's suggestion of a method of approach to the recognition of the biologic false positive serologic tests for syphilis.

4. Clinical problems. Shaw's report of 70 patients exhibiting cutaneous or mucous membrane syphilids or syphilis of the bones, or both, of which 15 (21 percent) had neuraxis involvement. Dyar and Dalton's description of 16 different manifestations of syphilis in the eye. Smith's report on the importance of syphilis in diseases of the nose and accessory sinuses. Williams and Kimmélsiel's report on syphilis of the

stomach. Cormia and Lewis' report of the factor of latency in syphilis. O'Leary and Williams' report on the duration of the infectiousness of syphilis.

5. Cardiovascular syphilis: Kampmeier and Combs' report on the prognosis in syphilitic aortic insufficiency, in which the authors evaluate factors other than antisyphilitic treatment.

6. Neurosyphilis: Kulchar's study of the advantages of cisternal puncture over lumbar punctures, and Emmett's discussion of "tabetic cord bladder."

7. Congenital syphilis: A new book by Dennie and Pakula, covering this subject efficiently and in more detail than has been attempted before. Black's condensation of his previous paper on the diagnosis of congenital syphilis. Hays' report on the role of syphilis in the production of mental deficiency. Supplement 7 to Venereal Disease Information entitled "Syphilis in Mother and Child," which covers the problems of syphilis in the pregnant woman and congenital syphilis. An editorial in the *American Journal of Syphilis, Gonorrhea and Venereal Diseases* on the oral treatment of syphilis in children. Christie's discussion of the value of the roentgenographic examination in the diagnosis of syphilis in newborn infants. Whitridge's report on changes in the long bones of newborn infants following administration of bismuth during pregnancy. Evans' discussion of some possible errors in the roentgen diagnosis of syphilis of the bones in infancy. The report of Kruse and associates on ocular manifestations of ariboflavinosis (and its relation to interstitial keratitis).

8. Therapy: A long-range comparison of malarial and artificial fever in the treatment of paresis by O'Leary and associates. A useful finding in the tempering effect of bismuth on therapeutic malaria reported by Brunsting and Love. The findings of these authors corroborated in another article by Cole and associates. A comparison of the results of treatment of neurosyphilis by tryparamide and by neocryl, reported by Ross. Report of the Council on Pharmacy and

Chemistry of the American Medical Association commending investigations made on massive dose intravenous chemotherapy of syphilis.

9. Treatment reactions: Report by Epstein of 2 patients with a history of plumbism who suffered recurrences following bismuth treatment for syphilis. "Mobilization of bismuth produced by ammonium chloride," reported by Corson and associates. Early acute arsenical erythemas ("erythema of the ninth day"), discussed by Thomas and Canizares. Blood dyscrasias following arsenical injections, studied by Falconer and Epstein. A review by Stephenson and Chambers of the toxic effects of arsenical compounds used by the United States Navy. The study of Schoch and associates of the use of mapharsen following dermatitis from arsphenamines. Rankin and Marlow's study of the extent of liver damage after recovery from post-arsphenamine jaundice. The effect of diet in guarding against liver damage from the arsphenamines reported by Messinger and Hawkins.

Lymphogranuloma venereum as a systemic disease. Report of a case with involvement of the skin and the eye. Tibor Benedek and Dora B. Olkon. *Am. J. Syph., Gonorr. & Ven. Dis., St. Louis*, 25: 28-47, Jan. 1941.

The authors survey the literature concerning skin manifestations caused by the virus of venereal lymphogranuloma.

They describe the case of a 44-year-old white man who had scattered papulopustular lesions on the trunks and shoulders with ulcerative lesions on the inside of both thighs near the inguinal region, on the scrotum, and on the anterior surface of the penis. There was no involvement of the regional lymph nodes. This patient had three recurrences of the ulcerative lesions, always on areas of the skin which had not been involved before. Simultaneously with the ulcerative skin lesions, an iritis developed which was attributed to the lymphogranuloma virus. The iritis reappeared three times in connection with the recurrence of the ulcerative

skin lesions. Miyagawa's elementary bodies (the virus of venereal lymphogranuloma) were demonstrated in sections of the ulcers by means of Giemsa stain and of Victoria blue 4 R stain.

The authors believe that the papulopustular and ulcerative lesions in connection with the recurrent iritis were due to a hematogenous distribution of the virus.

The varieties of skin eruptions in venereal lymphogranuloma reveal all the types of exanthems seen in connection with deepseated suppurative mycosis of the skin, such as trichophytids, microsporids, and favids. The authors state that these latter occur by hematogenous transport of the fungus elements from a primary focus into a skin already sensitized to the fungus. It is known that these "ids" may occur spontaneously. Often, however, they are first elicited by X-ray irradiation of the primary focus or following the administration of an intracutaneous injection of trichophytin.

According to the authors, there is no doubt that the virus of venereal lymphogranuloma is present in the skin eruptions. Midana, Peruccio, and others proved it biologically. Benedek and Olkon demonstrated it in histologic sections by means of special staining.

Although there is no evidence to date that the virus has been demonstrated in the circulating blood in human beings, the authors are convinced that this last and important link of evidence will be produced by finer developments of technic.

Thus, the authors conclude that venereal lymphogranuloma is in all its manifestations a systemic disease and not a local condition.

Cardiovascular syphilis. A clinical and electrocardiographic study. L. H. Berk. *New York State J. Med., New York*, 41: 223-233, Feb. 1, 1941.

The early diagnosis of both uncomplicated aortitis and coronary ostial stenosis is difficult, especially when the previous history and Wassermann reaction are negative. In most early uncomplicated

aortitis the electrocardiogram is normal and, in the author's experience, it becomes abnormal only when the process spreads to the valves or involves the coronary arteries. The electrocardiogram in the majority of cases of advanced cardiovascular syphilis shows quite marked pathologic changes that, though nonspecific, are of the greatest value both in diagnosis and prognosis of syphilitic heart disease. Taken in the usual manner the electrocardiogram is normal in 95 percent of the early cases.

Analysis has been made of 172 cases of cardiovascular syphilis which were admitted to the wards and to the cardiac clinic of Bellevue Hospital from 1932 to 1940. There were 20 cases of early and 117 cases of advanced cardiovascular syphilis, and 35 cases upon which an autopsy had been performed. There were 39 cases of uncomplicated aortitis, 23 cases of aneurysm, and 124 cases of aortic insufficiency.

In this group of 20 early cases only 5 percent showed a pathologic electrocardiogram before a graduated exercise test, whereas 25 percent showed an abnormal response to the exercise test. When the test is positive, the electrocardiogram shows characteristic upward or downward displacement of the RS-T junction and modifications of the RS-T segment in two or more leads, with changes in the initial deflection and ectopic beats.

The electrocardiographic study with the exercise test was performed in the controlled series of 50 cases under 45 years of age with presumably normal hearts or merely essential hypertension, and one positive result was obtained, while in the author's group of 20 cases of early cardiovascular syphilis of corresponding age and sex, 5 positive exercise tests were observed. Before the exertion test in 7 cases of aortic insufficiency, 5 were normal electrocardiographically. Following exercise, however, marked pathologic changes were noted. In 2 cases, the ST₁ and ST₂ were negative and the ST₃ positive; in 2 others, the ST₂ and ST₃ were negative; while in the remaining case, the

ST₃ alone was negative. All of these showed in addition numerous extra systoles from ectopic foci.

A positive test with or without angipectoris in a syphilitic under 45 years of age is strongly suggestive of aortitis with involvement of coronary orifice. After 50, a positive test with or without the presence of cardiac pain is due rather to coronary sclerosis on an inactive syphilitic basis. Although the diagnosis of cardiovascular syphilis is not justified on the basis of electrocardiographic findings alone, the presence of a pathologic electrocardiogram with a positive exercise test is at present, the author believes, the only safe method of establishing the diagnosis of aortitis with coronary ostia stenosis at an early stage.

TREATMENT

Toxicity of sulphathiazole. *Lancet*, London, 1: 49, Jan. 11, 1941.

Moerschlin and Hurschler (Schweiz med. Wchenschr., Oct. 12, 1940, p. 972) claim that sulfathiazole is much less toxic for red cells than sulfapyridine. Their evidence is indirect. They noticed that in the blood of about 50 percent of patients receiving sulfapyridine some of the erythrocytes, when stained supravitaly with cresyl blue, showed a definite intracorpuseular granule situated as a rule at the periphery of the cell. These granules were sometimes, but not commonly, found in reticulocytes. In patients treated with sulfathiazole, however, the red cells did not show these granules at all. To confirm this observation, they gave the two drugs to groups of white mice. Sulfapyridine produced these granules in the red cells of about 75 percent of the animals, and the percentage of affected red cells ran roughly parallel with the size of the dose. However, sulfathiazole, even in much larger doses and given for long periods, did not cause the granules to appear. The na-

ture of these intracorpuseular granules is not known, but they have been found when methemoglobin formation has occurred and they may be produced by hemolytic drugs such as phenylhydrazine. They seem to be definitely connected with the toxic action of drugs on the red cells. Hence, Moeschlin and Hurschler conclude that sulfathiazole is less toxic than sulfapyridine.

Sulfathiazole is excreted more rapidly than sulfapyridine and the maximum concentration of sulfathiazole in the serum is neither so high nor maintained for so long as that of sulfapyridine. Moeschlin and Hurschler consider these points but do not think they are decisive. They prefer a chemical explanation and suggest that the absence of the pyridine ring may make sulfathiazole less toxic to red cells.

The question of the liability of sulfamide drugs to produce methemoglobin has been investigated by Rimington and Hemmings (*Biochem. J.*, 33: 960, 1939). They noticed that, as a rule, substances which produced porphyrinuria were also capable of producing methemoglobin in vivo. After examining several of these and related substances they concluded that it was the presence of a free, or potentially free, aromatic amino group that determined whether a drug could produce methemoglobin and was therefore liable to be toxic. They did not examine sulfathiazole, but since it has a free aromatic amino group like sulfapyridine, it is by this criterion also likely to be toxic.

The explanation of sulfathiazole's diminished toxicity is not yet settled, and it seems premature to recommend, as Moeschlin and Hurschler do, the wholesale substitution of it for sulfapyridine in all but a few special cases. A better course seems to be that recommended by Paisford and Whitelaw (*Lancet*, 2: 451, 1940) in the treatment of pneumonia—to give sulfapyridine at first in order to get the maximum concentration in the serum as soon as possible, and then gradually replace the sulfapyridine by sulfathiazole in subsequent doses. This mode of

treatment exploits the pharmacologic advantages of both drugs.

The surgical treatment of syphilitic optic atrophy due to chiasmal arachnoiditis.

Louis Hausman. *Am. J. Ophth.*, St. Louis, 24: 119-132, Feb. 1941.

The syndrome of failing vision and primary optic atrophy due to syphilitic arachnoiditis of the optic chiasm and nerves was first reported in 1937. Six cases have thus far been studied. In three of them craniotomy was performed, and in each instance adhesions were found and removed from the optic chiasm and nerves. These three cases are considered in this report. Clinically they were characterized by progressive loss of vision culminating rapidly in complete or partial blindness, primary optic atrophy, and evidence of syphilis.

CASE 1 (the case reported in 1937). At the time of operation the left eye was blind and the right showed a temporal hemianopsia with great reduction in visual acuity. Color vision was lost in both eyes. Craniotomy was performed and exploration revealed dense adhesions around the optic chiasm and nerve. Soon after these were freed vision began to return. Two years after operation, the end result as to the restoration of vision is excellent for the patient has retained all her gains without any relapse. Visual fields have expanded and visual acuity is 16/15 in one eye and 16/15-2 in the other. Color vision for red and blue has also returned.

CASE 6. At the time of operation the left eye had been completely blind for 8 years except for a small sector of light perception; the vision in the other eye was so impaired that the perimetric studies could not be used for localization of the lesion. Since the loss of vision had continued despite intensive antisyphilitic treatment, a craniotomy was performed. Adhesions were found around the optic chiasm, and the left optic nerve was found markedly atrophied. About 5½ months after operation the acuity in the right eye, blind 5 years, had so improved

that the patient could read the "40" line of the Snellen chart at 20 cm.; the color vision for red and blue had also returned.

CASE 7. At operation visual acuity in both eyes was so reduced that the patient could not get about by herself. Exploration after craniotomy revealed adhesions around the optic chiasm and nerves, and these were liberated. Improvement set in gradually; about 1½ months after operation, the light fields showed marked expansion in both eyes. The patient no longer needs a constant escort.

Each of these cases presented serologic evidence of syphilis in the blood, spinal fluid, or both, at some time. The colloidal gold curve in case 1 was 0011221100; in case 6, 0111100000; in case 7, 1344221100. A diagnosis had previously been given of tabetic optic atrophy. In cases 1 and 7 there was no clinical evidence of tabes in the spinal cord.

There are certain signs which aid in the diagnosis of syphilitic chiasmal arachnoiditis. When patients with syphilis and primary optic atrophy present heteronymous visual field defects, or multiple cranial nerve lesions adjacent to the optic nerve, or when primary optic atrophy and syphilis are the only signs present, adhesions at the base of the brain in the region of the chiasm should be suspected. When adequate antisymphilitic treatment in a case of syphilitic primary optic atrophy fails to arrest the progress of visual impairment so that blindness threatens, even severe optic atrophy is no contraindication to surgery. When blindness is imminent no reasonable therapeutic measure should be ignored.

On the value of sulfanilylaminopyridine in the treatment of gonorrhea. S. v. Pastinszky. *Wien. med. Wchnschr.*, 90: 550-555, July 27, 1940.

Sulfanilylaminopyridine was used in the treatment of 106 men with gonorrhea. The dosage consisted of 2 tablets 3 times a day for 4 days followed by a rest period of 6 or 7 days. Local treat-

ment was also given. Cures were obtained in 88.6 percent of cases (66 percent after 1 course, 17.9 percent after 2, and 4.7 percent after 3 courses). The average duration of treatment was 50 days as compared to 50 or 60 days with the old type of therapy. Acute anterior urethritis responded best to treatment with 96.8 percent of cures. In cases with acute epididymitis 72.7 percent cures, in acute prostatitis 71.4 percent cures, and in chronic prostatitis 80 percent cures were obtained. In complicated cases vaccine therapy as well as special local therapy is indicated in addition to chemotherapy.

The side effects consisted of headache and malaise (35 percent of cases) and gastric disturbances (40 percent of cases). Catarrhal icterus occurred in 1 patient and mild photosensitivity in 1 patient. There was no significant effect on the number of erythrocytes or the color index. Two patients had slight leukopenia and 3 an increase in eosinophils. No unfavorable effect on spermatogenesis was observed.

Skin manifestations due to sulfanilamide and its derivatives. Arthur M. Greenwood. *New England J. Med.*, Boston 224: 237-238, Feb. 6, 1941.

Skin rashes occurring in the course of therapy with sulfanilamide or its derivatives are multiform in character and are not specific, with the exception of those following the use of sulfathiazole. They may be manifestations of toxemia, sensitization, or allergy. They may occur at any time in the course of treatment, but generally from the fourth to the fourteenth day, and in from 2 to 10 percent of the cases, depending on the intensity of treatment. They are likeliest to appear in areas exposed to sunlight and may be accompanied by an increase in the excretion of porphyrins. The occurrence of a rash is a warning of danger, and treatment with a sulfonamide should be stopped and not renewed unless the gravity of the case warrants it. If treatment is to be resumed

be patient should be tested for sensitivity with small doses of the drug.

In many cases the first manifestations of the toxic type of eruption due to overosage are shown by a faint, finely papular rash on the arms, perhaps accompanied by mild itching and fever. If the drug is continued, the rash spreads and becomes maculopapular, scarlatiniform, or morbilliform. It may involve the whole body or be limited to various parts. There is no lymphadenitis accompanying it. On discontinuing the drug, the fever goes and with it the rash, occasionally leaving the involved surfaces desquamating. In some cases the rash disappears even though the drug is continued. In others, after cessation of sulfanilamide and the disappearance of the rash, the drug may be resumed in moderate dosage without untoward symptoms. Such cases may be considered to be due to direct toxicity of the drug, either from primary overdosage or the patient or from accumulation. There is no allergy and no gradually built-up sensitization.

Patients who show a purely allergic reaction have, early in the course of administration of sulfanilamide, intense itching, sneezing, lachrymation, and dyspnea, with edema of the lips, eyelids, and face. The eruption may be urticarial, hemorrhagic, or bullous. Patch and scratch tests may be positive for the drug.

Allergotoxic effects, those caused by gradual sensitization, ordinarily appear later in the course of therapy, from the seventh to the fourteenth day of average dosage with sulfanilamide. The eruption is generally maculopapular and accompanied by pruritus and urticarial lesions, fever, and, in some cases, by leukocytosis. Resumption of sulfanilamide, after discontinuance of treatment and the disappearance of the rash, is quite certain to bring on a recurrence of the reaction.

Sulfanilamide rashes are multiform. They may be erythematous, papular, morbilliform, scarlatiniform, urticarial, petechial, or bullous. The mucous membranes may be affected. The rash may

be limited or general, accompanied or unaccompanied by fever and itching. Exfoliative dermatitis has been a sequel in some cases. One case has been reported in which a fixed eruption was produced by sulfanilamide and sulfapyridine. Most cases are maculopapular, not generalized, and are accompanied by fever and pruritus. The only difficulty in diagnosis is to distinguish the morbilliform type from measles and the scarlatiniform type from scarlet fever. The average interval between beginning administration of the drug and the appearance of the rash falls within the period of incubation of the common infectious fevers. With a morbilliform sulfanilamide rash, however, Koplik's spots, catarrhal symptoms, and lymphadenitis are not present. In a scarlatiniform sulfanilamide rash the characteristic tongue and throat of scarlet fever are absent.

Persons sensitive to local anesthetics and those who have had other drug rashes are likelier than others to be sensitive to sulfanilamide.

Treatment of paresis and tabes with roentgen rays. F. Bering. *Med. Welt*, Berlin, 14: 1066-1068, Oct. 19, 1940.

Roentgen-ray therapy was tried in patients with general paresis and tabes in whom malaria treatment was contraindicated. All parts of the head were exposed to the rays. According to the author there are no contraindications to this type of therapy since with the proper technic there is no danger. The disadvantage is temporary loss of hair. A total of 130 patients were treated. The therapeutic effects, according to the author, are comparable to those obtained with malaria. Some patients who had not responded to malaria treatment were consequently improved by roentgen-ray therapy. Another advantage of this treatment is that the patients do not have to be hospitalized.

In patients with tabes subjective and also objective disturbances were favorably influenced. The effect on the cerebrospinal fluid was better in paresis than in tabes.

A comparison between several arsphenamine derivatives. More rapid "military" or "port treatment" for syphilis. R. D. G. P. Simons. *Geneesk. tijdschr. v. Nederl.-Indië, Batavia*, 80: 2244-2260, Sept. 17, 1940.

A comparative study was made of neoarsphenamine, neoarsphenamine-Billon, solusalvarsan, alaphine, and mapharsen. The results obtained with the Netherlands alaphine and neoarsphenamine-Billon were apparently as satisfactory as those obtained with neoarsphenamine. Favorable results were also obtained with mapharsen whereas solusalvarsan was found to be much more toxic than the other preparations. It was found that neoarsphenamine, alaphine, and mapharsen could be injected daily without greatly increased risk of toxic reactions and with good results. The author recommends hyperintensive treatment in wartime and for the treatment of sailors. If toxic reactions occur, treatment should be changed to the classic type.

Round-table conference on recent advances in chemotherapy. The sulfanilamide-gonorrhea romance. Pelouze. *Pennsylvania M. J., Harrisburg*, 44: 586-587, Feb. 1941.

Pelouze explains what he calls the "sulfanilamide fiasco" by the fact that urologists had forgotten that the ways of gonorrhea easily fool the physician. They erroneously assumed, therefore, that every patient who eventually recovered from his gonorrhea did so because of sulfanilamide. As a result cure-rates of 50 to 90 percent or more were claimed, whereas a generous scientific estimate should have given not more than 30 percent. Sulfanilamide is now proven to be the least effective of the three sulfonamides, and many investigators believe that it should not be employed for any type of gonorrhea. It not only cures fewer patients but produces carriers at as high a rate as 20 percent. When these carriers transmit

the disease to other individuals most, if not all, of these persons become totally asymptomatic carriers. However, when in turn, they pass on the infection, the third party has frank gonorrhea.

By relying on the older, so-called tests of cure and a persistently clear urine for 2 weeks or longer, one gonococcus carrier out of every 3 cases will be sent into society. If most careful microscopic searches are added, the margin of error is only 1 out of 20; adding cultural studies, about 1 out of 100 will be missed.

There is ample experimental reason to believe that both sulfapyridine and sulfathiazole will give higher cure-rates than sulfanilamide. Some careful clinicians have attributed to both apparent cure-rates of from 80 to 90 percent. As sulfathiazole is far less toxic it is obviously the best and safest drug. In the treatment of urogenital gonorrhea high blood concentration is not a factor of any importance; some of the best results have occurred where this concentration was never higher than 1.5 mg. per 100 cc of blood, and some of the most dismal failures have occurred in patients where it reached 15.0 mg. Thus, high dosage is not needed. The treatment may be started with 3.0 gm. per day, reducing the dosage to 2.0 gm. after the first 3 days, and as good results will be obtained as are to be had with higher dosage. If the patient is not symptom free by the end of 5 days of medication he can safely be classed as a drug failure; after a few days' rest, another sulfonamide can be substituted. It is also scientifically safe to say that if the patient is not cured by the end of 10 days the drug used will not cure him.

In order to have the real value of these drugs it will be necessary to keep patients under far better control than is now the case. At least 75 percent of these patients lapse treatment long before cure has taken place. In some dispensaries, this lapse rate is over 90 percent.

Fever therapy in diseases of the nervous system. Samuel H. Epstein and Harry C. Solomon. *M. Clin. North America*, Philadelphia, 24: 1555-1572, Sept. 1940.

In neurosyphilis the three outstanding factors relating to the mechanism of artificial fever therapy are: (1) The destruction of invading spirochetes by elevation of body temperatures; (2) the biologic response to nonspecific foreign protein shock; and (3) the alteration produced in the brain parenchyma by the malarial organism.

Malaria is well established throughout the world as standard treatment for parietic neurosyphilis. Since 1931 electropyrrexia has been used. Comparative evaluation of the two methods is difficult because there are hardly two groups of cases in literature that are comparable with each other. Electropyrrexia is indicated especially in the Negro race, many of whom are immune to malaria. Cardiac and renal diseases are contraindications to the use of malaria. The authors stress the value of the combination of tryparsamide with fever therapy. They say that tryparsamide is capable of producing beneficial results similar to those produced by malarial therapy and that a considerable number of preliminary tryparsamide injections greatly enhances the possibility of therapeutic success in the treatment of parietic neurosyphilis.

The therapeutic effect of fever upon the course of tabes dorsalis is not so striking. Serologic reversal is frequently accomplished but clinical cures are not easily forthcoming. In the authors' experience tabetics with cord bladders are prone to develop serious complications due to infection. Some relief in patients with gastric crises has been obtained. In optic atrophy malaria is of distinct value in arresting the progress of visual loss.

In early meningeal syphilis, neither tryparsamide nor fever therapy is advisable at the start of treatment, but may be used after 2 or 3 years of treatment in patients with resistant spinal fluid

serology. Only about a third of the patients with vascular neurosyphilis show good results. Malaria is contraindicated on account of the deleterious effects upon the circulatory system.

Accumulated clinical evidence indicates that fever therapy adequately prevents clinical neurosyphilis. Patients who receive adequate chemotherapy and later malaria treatment showed no clinical progression. Therefore in recent years, mechanical hyperpyrexia has been employed in asymptomatic neurosyphilis. The authors recommend, as the best method of treatment of resistant neurosyphilis, combined artificial fever therapy and chemotherapy.

The results of fever therapy in cases of juvenile paresis are not so favorable as in the acquired disease. The authors' experience with malaria in this disease has yielded unsatisfactory results, and this was true with electropyrrexia also. In a series of 30 cases of juvenile paresis, 3 patients developed interstitial keratitis subsequent to fever treatment and while receiving arsenical treatment, and 4 patients of the series of 9 cases of nonparetic congenital neurosyphilis, who were not given fever therapy, likewise developed interstitial keratitis. This would appear to be more than a coincidence. The hypothesis is advanced that the febrile condition enhances the possibility of the appearance of an interstitial keratitis (a gummatous lesion) in a patient with an essentially parenchymatous disease.

Temperature swing in the treatment of general paresis. Hypohyperthermia method. H. C. Solomon, I. Kopp and A. S. Rose. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 96-102, Jan. 1941.

The authors suggest that relatively wide swings of temperature may be an effective method for the treatment of syphilis of the central nervous system. They describe the method and the immediate effects of lowering body temperature to approximately 90° and then im-

mediately raising it to 104°, giving a temperature swing of approximately 14°.

In reducing the temperature of patients, the authors followed the technic of Fay. It was necessary to anesthetize the patients before applying cold to their bodies. Without anesthesia the patients were extremely uncomfortable, and shivering and other mechanisms were effective in holding their temperatures almost constant beyond the period of tolerance of the cold. When the patients were anesthetized, there was little or no shivering, and the temperatures fell promptly when the ice was placed about their bodies.

Pentothal sodium, administered intravenously, proved to be the most satisfactory anesthetic, because it produced anesthesia which was not too prolonged, yet sufficiently deep to eliminate muscular jerkings and shiverings. The only complication was thrombosis of those veins into which the drug had been injected, which occurred in an unfortunately high percentage of the cases.

A summary of the technic is as follows: (1) The patient is prepared by a cleansing enema on the evening before, and by the omission of breakfast. (2) After a period of 10 or 15 minutes for stabilization of the temperature, 7 to 10 grains of pentothal sodium is injected slowly. (3) Approximately 100 pounds of finely cracked or shaved ice is placed about the patient from the axillae to below the knees, excluding the back. One arm is kept exposed for blood pressure readings and subsequent venipunctures. (4) More pentothal is injected from time to time in decreasing doses to maintain the anesthesia. (5) When the temperature falls to the desired level, the ice is removed, the body surface is dried, warm blankets are applied, the cabinet cover is lowered, and the heat turned on. (6) After the patient's temperature begins to rise, the inductotherm is turned on and the cabinet temperature maintained at 102° to 105° F. until the patient's rectal temperature reaches the desired level above normal. (7) The cabinet is then opened, and the body

temperature is allowed to return to normal.

In the patients treated thus, the swing of temperature from normal to approximately 90° F. and from 90° F. to 104° or 105° F. and back to normal was readily effected and caused no noteworthy disturbance. A few hours after the conclusion of treatment such patients were able to be up and about with apparently no delayed symptoms or discomfort.

The dulling of the cerebral centers by the anesthetic during the uncomfortable period of recovery of body temperature was not the only fortunate effect observed. The discomfort ordinarily felt by a patient when his temperature was raised above normal by physical methods was considerably less after the cooling process than when he started an upward rise in temperature from the normal level. This factor could not be measured, but it was observed in every case.

Eight patients were treated in this manner (a total of 37 treatments). It is impossible to draw any definite conclusions yet as to the efficacy of this temperature-swing method in comparison with the ordinary fever treatment. A year or two of observation of a large group of patients will be required before any definite therapeutic conclusions will be justified.

Dangers of sulphapyridine. A. W. Frankland. *Brit. M. J.*, London, 1: 32, Jan. 4, 1941.

In this letter to the editor the author says that he does not agree with Corfield's statement (*Brit. M. J.*, 2: 682, Nov. 16, 1940) that sulfapyridine soluble can be injected into the gluteal muscles without any particular precautions.

If given subcutaneously ulceration of the skin with a persistent sinus results. If given deeply there is a grave danger that one of the larger branches of the sciatic nerve will be involved. The author says that he has seen six cases of foot drop with varying degrees of anesthesia result from this accident. Although most patients showed varying degrees of recovery, often with intensely painful

muscles, one patient showed almost complete foot drop after 3 months. In another case, gluteal paresis developed, so that the patient was unable to fix the pelvis 3 months after receiving the injection. Children seem particularly liable to have gluteal weakness due to the motor nerve being partially or completely destroyed. As long as the affected muscle responds to faradism a nearly complete recovery appears to take place. Unless there is a good and plentiful blood supply to the part injected no absorption takes place, so that destruction of the adjacent tissue begins. Microscopically, at first, there is what appears to be a hyalinization of the cells where the solution has reached. If the blood supply is good the fluid is absorbed and the cells ultimately recover, but if the blood supply is bad the cells undergo necrosis and later fibrosis.

The author believes that 3 cc. is the maximum amount of sulfapyridine soluble that should ever be used in one place at one time, because the body is unable to absorb more, and instead of its being absorbed it destroys the adjacent tissues. This amount (3 cc.) is probably a dangerous amount to give to a child.

Intramuscular injections of the drug should be given only in an emergency while arrangements are being made to administer it intravenously. It should be given only when the patient cannot absorb the drug from the stomach or if a high concentration is required. Though crippling dangers are rare at present, this is no excuse for not knowing that they may occur, especially when with the increasing use of the intramuscular route in inexperienced hands they will become more common.

Syphilis in the pregnant woman. Mortimer D. Speiser. *New York State J. Med.*, New York, 41: 240-246, Feb. 1, 1941.

A special prenatal syphilis clinic was organized at Bellevue Hospital 6 years ago. In the last 16,437 deliveries at Bellevue Hospital there were 790 cases diagnosed as having syphilis, an incidence of

4.8 percent. After an evaluation of the patient's history, the physical examination, and serologic tests, a total of 632 cases were chosen for study—580 classified as acquired syphilis and 52 as definitely or possibly congenital syphilis.

Previous therapy was admitted in 57.2 percent of the acquired cases; in 21.2 percent there was a history suggestive of early manifestations, and in 1.4 percent of late. In only 9 percent was a history obtained of known syphilitic offspring who had either died as a result of their infection or were under treatment. Late abortions, premature deliveries, and term stillbirths occurred in 18.8 percent of the cases, and in 24.7 percent no significant data could be elicited in the history regarding a previous syphilitic infection.

In the congenital group a history of treatment was obtained in 65 percent of the cases, while 88 percent gave a history of previous lesions suggestive of syphilis. The physical examination at the time of admission revealed early syphilitic lesions in 8.1 percent of the patients and late lesions in 3.3 percent. Therefore, 88.6 percent of the patients with acquired syphilis were clinically latent. In the congenital group, manifestations were present in 65 percent.

The value of serologic tests in establishing the diagnosis of syphilis is shown by the results of the tests in these cases. At Bellevue Hospital only the complement fixation test is employed, using both alcoholic and cholesterinized antigens. In 24.7 percent of the cases the diagnosis was established on repeated positive reactions. In 37.6 percent there was a strongly positive reaction as well as a highly significant or suggestive history. In 16.5 percent there was a positive reaction with associated physical findings, while in 21.2 percent there was a negative or equivocal reaction with a history of previous treatment.

While the effect of pregnancy upon syphilis offers a field for continued observation there is little doubt as to the disastrous effect of syphilis upon pregnancy. There were 95 untreated mothers with syphilis who delivered 97 babies,

and premature termination occurred in 51.5 percent of the cases. In 81.5 percent there were deaths due to syphilis or live born babies with syphilis, while only 13.4 percent were free from the disease. Faulty presentation occurred in 12.4 percent. In patients with early lesions who had received no treatment, 54 percent had a morbid post partum course. In the entire untreated group, the morbidity was 23.1 percent.

A total of 566 cases were studied from the standpoint of the effect of syphilis upon pregnancy and the value of treatment. There were 517 babies delivered of 512 mothers who had acquired syphilis. Treatment given only during pregnancy salvaged 61.9 percent of the babies, while treatment given both before and during pregnancy saved 92.1 percent of the babies. A disastrous result in the latter group occurred in only 4.1 percent while in the former group it occurred in 25 percent. Where treatment was started any time after the sixteenth week of gestation even in the absence of previous therapy, the incidence of prematurity was reduced to 14 percent, disastrous results occurred in 29.5 percent, and 55.6 percent were free of the disease.

The treatment of the syphilitic prenatal patient depends upon the absence of medical and obstetric contraindications, the stage of the syphilitic process, the length of gestation, and the tolerance for the drugs employed. A definite conclusion as to the status of the newborn child often cannot be reached before it is discharged from the hospital. Treatment should be withheld until a definite diagnosis is established.

Massive arsenotherapy in syphilis. Brit. M. J., London, 2: 911, Dec. 28, 1940.

The author discusses the intravenous drip method of administering arsenical treatment for syphilis and quotes the statistics on results of such treatment (previously published).

He states that the action of such treatment seems to be analogous to that of sulfanilamide. That is, it depends

on the maintenance of an adequate concentration of the drug in the tissues over a sufficient period.

Massive arsenotherapy seems to give results as satisfactory as standard methods, does not unduly upset the patients, and under hospital conditions seems to be practical. If a patient is cured in 5 days instead of a year there is a big saving in time, and he is kept under control during the contagious stage of the disease. For these reasons it seems to be particularly applicable to military service (British) patients.

It is, however, doubtful whether any large proportion of civilian patients could be persuaded to stay in a hospital for the necessary period, when (under ordinary methods of treatment) they could carry on their work and have their treatment at the same time, attending a clinic perhaps once a week. It is open to question whether hospitalization of patients is economically sound. If the method became general a large number of beds would be required, so that it is doubtful whether there would be any saving in expense.

Until much more time has elapsed, and it can be proved that permanent cure results in a high proportion of cases, syphilologists will be wise to suspend judgment. It is desirable that some trial be made of the effect of massive therapy on syphilis in females and on the various forms of late syphilis, and also of the results to be obtained by including some form of bismuth in the treatment schedule.

A review of 58 cases of tabetic arthropathy. Maurice M. Pomeranz and Abraham S. Rothberg. Am. J. Syph., Honor. & Ven. Dis., St. Louis, 25: 103-119, Jan. 1941.

The authors review the cases of 58 patients with tabetic arthropathy. The largest number of cases occurred during the fifth and sixth decades of life. There were 42 males (average age, 43.5 years) and 16 females (average age, 51.0 years).

The knee joint was affected in 30 cases (38.5 percent), the hip in 14 (18.0 per-

cent), the tarsal joints in 15 (19.0 percent), the ankle in 6, the spine in 5, the toes in 3, the shoulder in 3, and the pelvis in 2 cases. Multiple involvement occurred in 19 cases. There were 12 instances of bilateral disease—the hips were affected in 3, the knees in 4, and the feet in 5 cases.

The authors believe that careful roentgenographic examination affords the most reliable means for diagnosis and frequently reveals an unsuspected neuroarthropathy. The neurologic examination is more frequently positive than the serologic tests and is therefore a more accurate guide in the diagnosis of this disorder. In the absence of clinical tabes the diagnosis of tabetic arthropathy depends upon the roentgenographic and serologic findings. Pain is usually present, but it disappears late in the disease.

In this series the blood Wassermann test was positive in 48 percent of the cases, and the spinal fluid was abnormal in 43 percent. The serologic tests were positive in 50 percent of the cases of patients with neurologic evidence of tabes.

In the early stages of the disease in these cases, rest in bed, traction, braces, or supports were employed. Repeated aspirations were performed in order to avoid distention of the joint with resulting relaxation or subluxation. In some of the cases conservative therapy had to be continued because of associated syphilitic disease or because of the fear of precipitating serious central nervous system complications following surgery. In spite of this precaution, one of the patients had delirium tremens, 2 became incontinent, and one had a postoperative intestinal obstruction.

The authors discuss the prognostic value of the clinical or roentgenologic estimate of the degree of fusion following arthrodesis. It is at times manifestly impossible to determine roentgenologically what fusion has occurred or to predict that it will be progressive. The altered appearance of the joint following surgery introduces confusing elements which nullify the usual criteria employed by roentgenologists to determine the pres-

ence of an ankylosing process. Clinically, likewise, such determination is not simple and is frequently misleading. The "practically completely fused" joints or those in which a "few degrees of motion exist" following arthrodesis and which are optimistically expected to progress to complete fusion frequently break down and become unstable joints. Thus, limitation of motion following arthrodesis is no indication that fusion is occurring or that a partially ankylosed joint will necessarily progress to complete fusion.

In this group of 58 cases, 21 operations were performed on 18 patients, 2 of whom died following knee fusions. Although a total of 11 fusion operations were performed, the only satisfactory results were obtained in the cervical spine and in a knee case. There were 2 fusion and 2 reconstruction operations on the hip, all of which were unsuccessful. (The authors state that it is fairly safe to predict that no hip joint can be successfully fused.) Fusion operations were performed on the knee joint in 8 cases with only 1 satisfactory result. In 1 synovectomy of the knee, pain became so agonizing that a low thigh amputation was necessary. Three amputations were performed because the extensive disorganization of the joints precluded any possibility of a satisfactory arthrodesis.

Gonococcal pelvic inflammation. James C. Goodwin. *Canad. M. A. J.*, Montreal, 44: 136-140, Feb. 1941.

The incidence of pelvic infection has been and should continue to be reduced with adequate modern gonorrheal therapy, including the use of sulfapyridine. In 110 cases of culturally proven gonorrhea in females recently treated at the clinic of the Toronto General Hospital no patient developed pelvic inflammation during or following ambulant treatment with sulfanilamide, disulfanilamide, or sulfapyridine. Four patients had shown evidence of beginning extension of gonococcal infection to the pelvis.

Gonococcal infection, whether in urethra and cervix or in the upper pelvic tissues, tends to become localized and self-

limited; it presents a remarkable tendency to resolve, often completely. Pelvic invasion of the gonococcus appears to be governed by factors associated with menstruation, unsatisfactory treatment, coitus, surgical interference with the cervix, and others, such as alcoholic excess, fatigue, malnutrition. Practically all initial attacks of gonococcal pelvic infection clinically tend to recover completely if recurrence can be prevented.

Sulfapyridine seems to be of value in limiting the extent and duration of pelvic infection. Surgical treatment, except for posterior colpotomy, should be reserved for the recurrent case, and then for the treatment of the sequelae of the infection rather than the infection itself.

PATHOLOGY

Syphilis of the eyes. Joseph Igersheimer. Proc. New York Soc. Clin. Ophth., Am. J. Ophth., Cincinnati, 24: 67-68, Jan. 1941.

Igersheimer stated that a change is occurring in the character of syphilis, as shown in a greater rarity of the tertiary and malignant forms. Due to early treatment even primary syphilis and the congenital form with its concomitant keratitis parenchymatosa are more rarely seen. Occasionally primary and tertiary affections of the lids, such as chancres and a mucopurulent conjunctivitis in which spirochetes are found, are seen in infants.

In experimental keratitis what appears to be fine precipitates are mostly new formations on the endothelium and often give rise to ruptures of Descemet's membrane and an inflammatory reaction in the deeper corneal layers. Just as in the advanced stages of the human type, experimental keratitis does not respond to anti-syphilitic therapy. In the acquired types it has frequently been shown that there is a history of congenital syphilis. In

keratitis pustuliformis profunda, though no spirochetes are found, there is always a positive Wassermann, and usually anti-syphilitic therapy is effective.

It is possible to have a syphilitic iritis without nodules. Not infrequently there is also pathologic change in the rest of the uvea, retina, and papilla along with the iritis. Retinal changes may occur without involvement of the choroid. Syphilitic papillitis may occur in various forms.

In optic atrophy associated with tabes and paresis, as soon as pallor of the disc occurs visual-field changes are always demonstrable, and dark adaptation is usually affected. Attempts have been made to traumatize the cornea of rabbits that have been injected with spirochetes but it was not possible to produce an interstitial keratitis. The only way the second eye may become infected is through sympathetic irritation. Cases of iritis with a gelatinous exudate are more typical of a gonorrheal than a syphilitic infection.

LABORATORY RESEARCH

On changes in the blood picture produced by diseptal C. O. Hrad. Dermat. Wehnschr., Berlin, 111: 1018-1023 Nov. 30, 1940.

Diseptal C was used in the treatment of 46 patients. A course of treatment consisted of 3 daily doses of 0.5 gm. at intervals of 8 hours for 5 days (total 7.5 gm.). Not more than 3 courses were given and these were separated by 5-day rest periods. The men received local treatment, the women only cleansing irrigations. The therapeutic effects were similar to those reported by Fuhs and Volavsek for uliron, and the side effects were no more frequent than with other sulfanilamides.

Blood was taken from each patient in a fasting state before, during, and after

each course. The erythrocyte picture either in regard to number or form showed no abnormalities. The leukocytes increased during treatment to return to normal or below the normal values at the end of treatment. The differential leukocyte count showed in some cases a slight shift to the left and also a definite increase of lymphocytes during treatment with a return to normal after treatment was stopped. The patients showing these findings were all acute cases who responded promptly to treatment and among whom no recurrences were noted.

Among a group of patients who had a history of previous gonorrheal infection and some of whom had complications, the complement fixation reaction or gonorrhea (Müller-Oppenheim) was invariably positive. In this group no change from normal in the erythrocyte picture was observed. Leukocytosis was very slight and there was no increase in the number of lymphocytes.

In a group of patients who required two or three courses of drug therapy a decreased blood sedimentation rate was observed, and the erythrocyte and hemoglobin values were lower than in the other groups. Two cases of fever and urticarial exanthemata were observed in this group. The leukocyte counts in this group increased in some patients during the second and third courses, remained the same in others, and decreased in some. The lymphocyte values increased during the second or third course.

Sulfapyridine and vomiting. An experimental study of the mechanism in the dog. Joseph F. Sadusk Jr., John W. Hirshfeld and Anne Seymour. *Yale J. Biol. & Med.*, New Haven, 13: 351-362, Jan. 1941.

Following the intravenous injection of a 5-percent solution of sodium sulfapyridine, dogs were found to vomit at a sulfapyridine concentration in the blood from 17 to 36.5 mg. percent. Occasionally dogs were found that did not vomit but exhibited signs of central nervous system intoxication when the blood

sulfapyridine reached a sufficiently high level.

Sulfapyridine was readily excreted into the stomach after the intravenous injection of a 5-percent solution of sodium sulfapyridine.

Removal of the stomach, and even of the entire gastrointestinal tract including the spleen and the greater part of the pancreas, did not inhibit the act of vomiting when sodium sulfapyridine was given intravenously in dogs.

Direct application of sulfapyridine, in a concentration as high as 100 mg. percent, to the vomiting center did not cause vomiting, whereas similar application of apomorphine to the vomiting center did cause emesis.

These facts indicate that sulfapyridine vomiting in dogs is not due either to local action in the stomach or to direct action upon the vomiting center. They further suggest that the vomiting is mediated through a reflex stimulation of the vomiting center, which certainly is not exclusively from the gastrointestinal tract but may arise from some other site or sites.

Studies on the pharmacology of sulfapyridine and sulfathiazole. The absorption of the free acid, the sodium salt and the glucoside from the alimentary tract. O. W. Barlow and D. R. Klimenko. *J. A. M. A.*, Chicago, 116: 282-286, Jan. 25, 1941.

The authors believed that the differences in rate of absorption of the various forms of sulfapyridine and sulfathiazole which they had found from other studies were of sufficient practical importance to warrant careful examination. The sodium salts and the free acids of these drugs were administered by means of a stomach tube to a series of nine normal adult monkeys and also to a group of six normal men. A similar study on the glucose derivatives and on the simultaneous administration of antacids was also made. Tables are given showing in detail blood concentrations for the monkeys, and blood concentra-

tions, urinary and fecal excretions for the men.

It was found that the sodium salts of sulfapyridine and sulfathiazole were absorbed from the gastrointestinal tracts of man and monkey more rapidly than the respective free acids. The glucosides were absorbed from the gastrointestinal tract of man, dogs, and rats less rapidly than the respective free acids. The simultaneous administration of alkali in the form of sodium bicarbonate or magnesium oxide with sulfathiazole hastened the absorption from the gastrointestinal tract of man. In rate and degree, conjugation of sulfapyridine was higher than that of sulfathiazole in man and monkey. Following the oral administration of equal doses, the blood concentration of unconjugated sulfapyridine was practically the same as that of unconjugated sulfathiazole. The total blood concentration of sulfapyridine, however, was higher than the blood concentration of sulfathiazole.

The results of this study support the observations on the absorption and excretion of the sodium salt of sulfapyridine in man recently published by Ratish, Davidson and Bullowa, except for their conclusion that there is less acetylation following the administration of sodium sulfapyridine than after the administration of the same quantity of the drug as the free acid.

Enhancement of certain toxic effects of codeine and morphine by sulfapyridine.

Susi Glaubach. *Proc. Soc. Exper. Biol. & Med., Utica*, 46: 53-57, Jan. 1941.

Experiments with codeine were performed on rats, mice, and rabbits, and with morphine on mice only. The results reported show that the effect of both codeine and morphine was enhanced by sulfapyridine. The increased activity of the drugs after administration of sulfapyridine becomes evident not only in the prolongation of their action but also in the intensity of their effects and in the increase of their toxicity.

Physical-chemical studies of the Müller conglobation reaction. W. Fröhlich *Arch. f. Dermat. u. Syph., Berlin*, 180 109-110, Apr. 20, 1940.

By means of the antigen used in the Müller conglobation reaction for syphilis, studies were made for the purpose of determining the role of cholesterol in the flocculation reactions.

When to alcoholic solutions of heart lipid increasing amounts of cholesterol are added and diluted with physiological salt solution, a characteristic curve with two precipitation optima results. The first occurs with a low cholesterol concentration corresponding to that used in most of the other flocculation reactions. The picture of the zone of the second precipitation optimum is characterized by the formation of regular streaks which give the antigen the appearance of silk. Microscopic examination in the dark field in this zone shows long, typical cholesterol needles to which heart lipid adheres in the form of tiny round balls, often completely covering the needles. The cholesterol causes no potentiometric change in the heart lipid in the mixture.

This condensation of the antigen on the surface of the cholesterol crystals produced (a) an increased concentration of the antigen and (b) the formation of (because of their size) easily precipitated particles and explains the fact that heart extracts with a high cholesterol content require little serum for the test. The maximum concentration of cholesterol is determined by the limited solubility of cholesterol in alcohol.

An attempt was made to produce conglobation by adding cholesterol to antigen serum mixtures. This attempt failed but gave an unexpected result. Occasional negative scrums showed definite flocculation. Preliminary experiments showed that syphilis-negative serums did not combine with heart lipid at higher salt concentration (3 to 5 percent) as do syphilitic serum

From these findings a new reaction was developed: 0.6 cc. of a 3- to 5-percent salt solution, 3 to 5 drops of active serum, increasing amounts of a selected heart lipid are incubated at 37° C. for 2 to 3 hours or are kept in the water bath for 1 hour. Then a 0.1-percent cholesterinsol is added, the mixture shaken for a short period of time and then allowed to stand for ½ hour. A 1/10 solution of hydrochloric acid containing acetone is added drop by drop. The following result is obtained: The syphilitic serums remain clear or show only slight opalescence. Negative serums show definite flocculation.

The author states that the explanation for the reaction might be that in the negative cases the heart lipid which, because of the high salt-concentration does not combine with the syphilis negative serum, is adsorbed by the cholesterol and precipitated by the acid and acetone at suitable pH. Further studies are in progress.

On the flocculating power of antigens extracted with alcohol from normal dried serums as compared to syphilitic serums. E. Cappelli. *Gior. ital. di dermat. e. sif.*, Milano, 81: 859-863, Oct. 1940.

This study is a continuation of previously published work in which the author was able to show that a positive Wassermann reaction could be obtained with syphilitic, seropositive serums by means of alcoholic extracts made from dried normal serum or from Wassermann-positive syphilitic serum. The flocculating power of these antigens with normal and seropositive syphilitic serums was investigated. With these antigens definite macroscopic flocculation reactions were produced with Wassermann-positive syphilitic serums. The author also found that the substances obtained by alcoholic extraction of normal serums were suitable for use as antigens both for complement fixation and flocculation reactions.

Reaction of sera from patients with yaws in quantitative complement-fixation tests for syphilis and tuberculosis. Elizabeth Maltaner. *Am. J. Trop. Med.*, Baltimore, 21: 145-150, Jan. 1941.

Yaws and syphilis present certain differences in the character and distribution of the disease processes upon which the clinical diagnosis is based, but the serologic reactions of these two diseases with the tests hitherto used do not differentiate them. Although the spirochetes causing the two infections appear similar in certain respects, their pathogenic activity in animals, as in man, differs to some extent.

A group of 44 specimens from patients with yaws were made available from Jamaica, British West Indies. Only one specimen was received from each case. Unfortunately the clinical data available were insufficient to permit detailed correlation with the results of tests. Among these specimens 41 serums reacted in the quantitative complement fixation test for syphilis, 35 with titers ranging from 10 to 400. The same linear relations between the reagents were observed as with syphilitic serum and the cholesterolized tissue extract antigen.

The absence of reaction in the other 3 cases was not explainable on the basis of the clinical data that were furnished. These cases were of 3 months' to several years' duration and all were said to present active lesions. Six patients had had no treatment; for 26 cases no information was given. This left 12 cases which had been variously treated, 5 having had 1 injection; one, 2; one, 3; one, 4; two, 6; one, 12; one, with a titer of 81, 14 injections. The findings in precipitation tests for syphilis with 3 highly reacting serums, titers of 251, 347, and 384 were of special interest. Only partial reactions were obtained with 2 each in the Kahn and Kline tests of the undiluted serum. However, when the serum was diluted and tested, marked precipitation occurred. This tendency to prozone reactions in precipitation tests has been noted

in other comparative series with highly active syphilitic serums.

Continued administration of sulfathiazole on renal and hepatic function in the dog. David R. Climenko, Evan W. McChesney and Frederick Messer. *Proc. Soc. Exper. Biol. & Med., Utica*, 46: 124-128, Jan. 1941.

The authors' purpose in this study was to ascertain whether or not the continued administration of large doses of sulfathiazole would result in a significant impairment of renal function, and, secondarily, to determine whether or not there is any alteration of the alkali reserve during such a regimen. Their conclusions were: (1) The continued administration of sulfathiazole to dogs over a period of 10 days in doses of 250 mg. per kg. per day produces a slight impairment of renal function as evidenced by elevation of the blood urea nitrogen level, and diminution in the urea clearance and P. S. P. excretion. (2) This impairment is reversible, and normal values are reestablished within 48 hours after the withdrawal of the drug. (3) Doses of this order have no demonstrable effect on O₂ capacity, O₂ and CO₂ content. (4) Such doses have no demonstrable effect on liver function as indicated by the rate of excretion of brom-sulfonphthalein.

A comparison of the Hinton, Kahn, Kline and Mazzini tests for syphilis. Edward L. Breazeale, Robert A. Greene and Harry B. Harding. *J. Lab. & Clin. Med., St. Louis*, 26: 637-643, Jan. 1941.

In the Arizona State Laboratory the Hinton, Kahn standard, and Kline diagnostic tests are performed on all blood specimens. Since it appeared that the Mazzini test might be a valuable addition to this procedure a comparison was made of these 4 tests upon 3,000 specimens. From the tables it is seen that there was a complete agreement of all 4 tests in 2,818 serums (93.93 percent) and a relative agreement in 2,858 (95.26 percent). In 1937 the authors reported a comparison of the Eagle, Ide, Kahn, Kline, and Laughlen tests, in which agreement was found in

98.5 to 99.5 percent. In this present study the percentage of agreement is slightly lower than in the 1937 report. Lack of agreement usually occurred in serums which gave doubtful or weakly positive reactions. In several cases, however, one or more of the tests gave strongly positive reactions, while others gave negative or doubtful ones. The authors feel that this failure to agree is due to two factors in the latter group: (1) A larger percentage of specimens from treated, latent, and congenital cases. (2) More specimens are being submitted for the laboratory diagnosis of syphilis, and a large percentage are from cases of chronic, undiagnosed illnesses.

In addition to the results given above, the Kline and Mazzini tests were employed as "screening tests" in a series of 1,042 specimens from the group of college students. Complete agreement in this series was 99.51 percent; relative agreement was 99.80 percent.

It was shown that the Kline, Kahn, and Hinton tests gave approximately the same number of negative reactions and that the Mazzini test gave fewer negative and more positive reactions. This was to be expected since the sensitivity of the Mazzini test is of the same order as the Kline exclusion test.

These results confirm the findings of Mazzini and Giordano as to the specificity and sensitivity of the Mazzini test. The authors believe that the Mazzini test is an excellent one for the laboratory diagnosis of syphilis.

A comparison of the response of yaws and syphilis in the rabbit to therapy with mapharsen and neoarsphenamine. B. J. Longley, N. M. Clausen and A. L. Tatum. *J. Pharmacol. & Exper. Therap., Baltimore*, 71: 49-51, Jan 1941.

The comparative response of rabbit yaws and rabbit syphilis to therapy with single doses of mapharsen and neoarsphenamine has been determined, and from the data obtained it appears that there is no essential difference in the

ease with which the two diseases may be cured.

Testicular transfer was the criterion of cure. The findings indicated that the therapeutic index of single doses of nearsphenamine is superior to that of single doses of mapharsen in the treatment of rabbit yaws and rabbit syphilis. The data should be read in the light of previously published evidence that multiple doses of mapharsen are considerably more efficient than single doses whereas, according to Kolmer, nearsphenamine is relatively less efficient. Consequently the significance of this contribution resides in its bearing on relative curability of yaws and syphilis and not on the determination of conditions for the development of maximal therapeutic efficiencies.

The absence of heterophile antibodies in cow sera and the occurrence of positive Kline reactions. Robert A. Greene and Harry B. Harding. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 89-92, Jan. 1941.

Kahn has said, "Some physicians believe that positive serologic reactions in the absence of syphilis are related to the presence of heterophile antibodies in the blood stream. In infectious mononucleosis, for example, there generally exists some parallelism between positive serologic reaction and the antibody titer against sheep cells. The extent to which such parallelism between heterophile antibody and positive serologic reaction exists in other pathologic conditions or under normal conditions has not been established."

The authors state that since cow serums usually give a high percentage of positive reactions to serologic tests for syphilis, they were interested in determining whether these reactions given by cow serums might be due to the presence of heterophile antibodies. In a series of 134 cow serums tested, 100 percent gave positive Kline reactions. Twenty-five (18.7 percent) of these agglutinated sheep erythrocytes, usually in low titers, so that 109 (81.3 percent) did not contain sheep heterophile antibodies. The

antisheep agglutinin was absorbed by guinea pig kidney and boiled beef red cells.

According to the authors, there was no correlation between positive Kline reactions and heterophile antibodies. They state that it seems probable that the substance in cow serums which gives rise to positive Kline reactions is different from that present in the serums of patients suffering from infectious mononucleosis.

Results obtained with the Kolmer, Kahn, Kline, and Eagle tests on animal sera.

N. P. Sherwood, Glenn C. Bond and H. F. Clark. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 93-95, Jan. 1941.

The purpose of this study is to ascertain the proportion of animal serums which give positive results when tested by a standard complement fixation and several flocculation procedures used in the serodiagnosis of syphilis.

The number of serums studied and the animals from which they were taken are as follows: 124 from beef, 4 from calves, 15 from horses, 6 from adult dogs, 8 from pups, 9 from cats, 1 from an opossum, 35 from rabbits, 16 from guinea pigs, 19 from sheep, 10 from chickens, and 12 from snakes.

The results obtained with the several tests varied enormously from species to species. Discrepant results were obtained in a single species with different tests. These facts at first suggested that the reactive factor of these serums might differ qualitatively from that present in the serum of syphilitic patients. The floccules formed on the addition of beef serum to Kahn's antigen failed to fix complement, unlike similar floccules obtained with syphilitic serum. However, floccules formed by horse and rabbit serum did fix complement, and in that respect the serums were indistinguishable from syphilitic serum. Like syphilitic serum, the reactive factor of beef and horse serum was associated with the globulin fraction, and its activity was markedly decreased on heating at 65° C.

for 30 minutes. In view of the higher incidence of the reactive factor in beef as compared with calf serums (as judged by flocculation tests) and similar findings for dog and pup serums, respectively, an age factor may have to be considered in evaluating data on animal serums.

The large proportion of positive and doubtful reactions obtained in these animals suggests the possibility that a small (at present indeterminate) proportion of normal human beings may also contain reactive substances resembling the antibodies of syphilitic serum. Whether this is true and whether this reactive component of normal serum can be distinguished from the true antibody of syphilitic serum (as suggested by Witebsky) are matters for future study.

Chemotherapy and growth of gonococci.

W. Blauch. *Arch. f. Dermat. u. Syph.*, Berlin, 180: 105-109, Apr. 20, 1940.

The growth on horse blood cultures of normal gonococci was compared with that of gonococci originating from cases of gonorrhea which had received chemotherapy. The gonococci which had been damaged by uliron treatment showed degeneration forms after 8 to 12, or at the latest after 24 hours, whereas in the cultures of normal gonococci these involution forms were not observed for 2 or 3 days.

A comparison of the growth of gonococci on horse blood and human blood, the human blood having been obtained from nongonorrheal patients who had received uliron therapy, showed no differences. The Neumann culture plate was found to be more satisfactory than the human blood plate.

Under the influence of chemotherapy degeneration forms of the gonococcus could be found on the mucous membrane. From these degeneration forms typical gonococci could again be cultured. Because of this observation the author warns against discharging patients as cured who still have degeneration forms of gonococci in their smears.

PUBLIC HEALTH ADMINISTRATION

Venereal disease folders.

Two new folders have been released by the U. S. Public Health Service. No. 4, "The Doctor Says," outlines the importance of a blood test and a complete physical examination before marriage. No. 7, "Venereal Disease and National Defense," presents the essentials of a community control program as defined in the official policy of the Army, Navy, and Public Health Service.

A sample copy of each folder is being mailed to subscribers of Venereal Disease Information. Copies are for sale by the Superintendent of Documents, Washington, D. C. The price is \$1.00 per hundred. Orders should be mailed directly to the Superintendent of Documents, Washington, D. C.

Pharmacy cooperates. Joseph L. Stenek.

J. Social Hyg., New York, 27: 33-34, Jan. 1941.

The first meeting of the committee of the American Pharmaceutical Association and the American Social Hygiene Association to further cooperation between medicine and pharmacy in the fight against syphilis and gonorrhea was held April 24, 1940. To date, 20 State pharmaceutical associations have gone on record as supporting the venereal disease campaign. A survey made by Drug Topics, covering 58,066 druggists, placed the venereal disease campaign second in importance on the list of 16 resolutions acted on at State pharmaceutical association conventions.

Treatment of venereal disease by general practitioners. *Lancet*, London, 1: 27, Jan. 4, 1941.

Facilities for the treatment of venereal disease are required within easy reach of the large colonies of people now in rural

areas of England. The Minister of Health has considered the provision of mobile units and improvised treatment centers, and has decided (Circular 2226), after discussion with the British Medical Association, to enlist the help of general practitioners.

The Minister suggests that local health authorities select, from among the local practitioners with the necessary qualifications, the number of physicians required for these mobile units and treatment centers. Applicants must provide evidence that they have performed the following operations in the presence of the medical officer in charge of a venereal disease treatment center: (1) Spread microscopic slides with discharge from 12 patients (including 6 females) for examination of gonococci. (2) Scraped 3 lesions suspected of being early syphilitic and collected the exuding tissue fluid in 12 capillary tubes. (3) Taken 6 specimens of blood. (4) Given 12 intravenous injections of neoarsphenamine or of stabilarsen and 12 intramuscular injections of bis-muth compound.

Practitioners who, in the opinion of the medical officer of health and the venereal disease specialist officer, are qualified by previous training to perform the above operations would be appointed without taking formal tests. Physicians who wish to qualify for service would be given training facilities at any treatment center. Those appointed would be supplied by the local authority, free of charge, with all necessary drugs, syringes, needles, and outfits for taking laboratory specimens. They would be required to keep simple records and to return these records to the venereal disease specialist. Fees would be 10s. 6d. for the initial attendance for diagnosis and treatment, and 7s. 6d. for every subsequent attendance or home visit. A transport allowance of 3d. a mile each way for each mile in excess of two would be granted.

It is suggested that any local council in England without a specialist venereal disease officer on its staff should appoint one,

perhaps on a part-time basis. This officer would supervise the treatment service, record-keeping, the treatment given, and the attendance of patients. He would be available as a consultant to practitioners serving under the scheme. These practitioners would be expected to inform him of any complicated case, and of any case requiring treatment at home, so that he might keep in touch with such patients from the outset.

During the war the expense of such services would be borne by a grant from the Exchequer. The Minister believes that a specialist venereal disease control officer will be of great help to each council in reviewing the needs of the area and suggesting plans to meet them.

Syphilis in industry. Albert E. Russell.
Bull. Genitoinfect. Dis., Boston, 4: 1-3, Jan. 1941.

The increased industrial activity in connection with the national defense program has acutely emphasized the necessity for maintaining a high health standard for workers. Machines, perfect as they may be, must have men with healthy bodies and minds to operate them. Syphilis is a disease that disables a person physically and mentally. To discharge a person with syphilis places a great burden on the worker, the community, and the Nation through denying him the right of an income. Without this, he will not have the treatment necessary to cure his disease, and in time he and his family may become public charges. Industry will pay for such cases of syphilis in added taxes.

A syphilis program reaching the more than 15 million people employed in the mining, mechanical, and metal trades and members of their families will include about half the population of the country. The industrial syphilis control program, therefore, is an integral part of the national program.

The industrial program may be carried out by several methods. The local health officer may take the initiative and in-

dustry may cooperate, or vice versa. In other cases, the workers may take the lead. In none of the plants cooperating with the Public Health Service are patients treated, but they are referred to their private physicians or to clinics. On the whole, these methods have worked out well. There have been some instances where education of the employer was necessary; many employers have thought that all syphilitic persons were infectious and should be avoided.

Intensive programs of case-holding coordinated with education measures will tend to decrease the spread of infection and to reduce the injurious consequences to the individual and the costs to society from general neglect of the disease.

Gonorrhea in arrested women. A contribution to the great significance of raids in the control of venereal diseases. H. Fischer and H. Gottschalk. *Sozialhyg. d. Geschlechtskr.*, supp. to *Dermat. Wehnschr.*, Berlin, 111: 1031-1033, Nov. 1940.

Among women admitted to the clinic because of gonorrhea or suspected gonorrhea 4 groups were differentiated: (1) Prostitutes appearing voluntarily, (2) arrested prostitutes, (3) other women appearing voluntarily, and (4) arrested other women. The fourth group is the chief object of the present study. The number of women in this group was found to have increased markedly in the period from 1935 to July 1940, whereas the number of prostitutes admitted in this interval decreased greatly. The increase from 1935 to 1940 was from 6 percent to 65 percent, and among these the number of infected women increased from 7 percent to 52 percent.

The most important cause for the increase in admissions of what might be called clandestine prostitutes were raids made in hotels, cafes, the main depot, and certain streets. Most of these women had neither work nor lodging. A smaller number of these women were located because they had been reported as sources of infection. During the 2-year period 63 percent of the women,

other than prostitutes brought in for examination, were taken in raids, and 58 percent of those found to be infected were taken in these raids.

During the year from July 1939 to June 1940, 116 arrested women (other than prostitutes) were found to have gonorrhea. Of this number 92 (79 percent) had gonorrhea at the time of admission, whereas the other 24 (21 percent) were found to be infected only after a certain period of observation. The usual observation period is 7 to 8 days during which two provocative treatments are given and following which a search for gonococci is made.

Building health defenses. Thomas Par-ran. *South. M. J.*, Birmingham, 34: 85-90, Jan. 1941.

The venereal diseases are of very great military importance. During the last war 6,804,818 days of service were lost in the U. S. Army because of venereal disease. This is equivalent to a year's continuous absence from duty of almost 20,000 men. In the Navy and the Marine Corps venereal disease accounted for 687,792 days lost from duty, which is equivalent to the absence from service of almost 1,900 men for a year. Because of the excellence of the Army and Navy medical corps this total was less than that suffered by the armed forces of any other nation engaged in the war. One of the public health mistakes of the United States at that time lay in the fact that funds, personnel, and facilities were not set up in time to protect the armed forces from infection during the training period. Substantial progress has been made since that time.

Every State now furnishes a free laboratory diagnostic service to all physicians. Expensive drugs for the treatment of patients are distributed to all physicians. In 2,887 clinics competent diagnostic and treatment service is available. In most of them, epidemiologic investigations are made to seek out sources of infection and bring them under treatment.

As a result of these efforts against venereal diseases, plus the more effective

modern chemotherapy of gonorrhea, a substantial decline can be recorded in new cases of syphilis and gonorrhea during the past year. Unless these efforts are redoubled, however, mobilization will reverse this favorable trend.

Realizing that control of venereal diseases among military forces requires coordination with civilian health authorities, an agreement has been reached between the U. S. Public Health Service and the War and Navy Departments concerning cooperative control measures. During extensive military maneuvers in 1939, an active campaign for health protection of the troops was carried out jointly by the military authorities, the U. S. Public Health Service, and the several State and local health agencies concerned. An example of the effectiveness with which this can be done is in Wisconsin where, during maneuvers involving 60,000 men over a period of 30 days, only four cases of gonorrhea occurred and not a single case of syphilis.

The problems of venereal disease control are not being handled as effectively in all areas as they were in Wisconsin. It is probable that large numbers of troops will be concentrated in the South. Many local authorities are tolerant of prostitution areas in which are found the foci of infection for a large part of the gonorrhea and syphilis occurring among troops and trainees.

Without civilian cooperation the Army can control conditions only on military reservations. Here is an opportunity to see how well democracy works by a demonstration of what realistic physicians, health officers, and local officials can do together to clean up this situation and to prevent disease at the source. From a purely practical point of view, it will pay to do it. The Veterans' Administration estimates that in the last 18 years, beginning 5 years after the war period, it has poured out at least \$82,000,000 in payment of compensation, benefits, medical care, and hospitalization caused by venereal diseases.

The incidence of syphilis in Puerto Rico.
Survey based on the results of complement fixation and flocculation tests in unselected and selected groups of the general population. O. Costa Mandry. Puerto Rico J. Pub. Health & Trop. Med., San Juan, 16: 203-236, Dec. 1940.

This is a report of the results of serologic tests on the blood (complement fixation and flocculation tests) of 32,305 persons (unselected) in Puerto Rico. Of these, 12,765 persons were from urban areas, and 19,540 were from rural sections of the island. The serologic test results in a selected group of 32,536 additional cases were also analyzed. This group was obtained from different institutions, hospitals, and routine laboratory tests.

Of the total of 32,305 unselected cases, there were 6.7 percent positive blood tests. Of the 19,540 persons from rural sections, 5.7 percent had positive tests. Of the 12,765 persons from urban areas, 8.6 percent had positive tests.

The percentage of positive tests was slightly greater among females than among males. In the age groups under 30 years the percentage was consistently higher for females than for males, while above 30 years of age the percentage was greater among males. The percentage among Negroes was about 3 percent greater than among white persons.

In the various age groups the highest percentage of positive tests (9.7) was obtained in the group above 45 years, while that in the group 15 to 24 years was only 5.8. The percentage in the group under 15 years was 6, while that in the group 25 to 34 years was 8.8 and in the group 35 to 44 years, 9.2.

Among 6,155 children and young adults in the public schools of Puerto Rico, picked at random, 5.6 percent had positive tests. Of 706 persons selected from the slums of San Juan (including all ages), 12.2 percent had positive tests.

Of 2,357 women attending health units of the Department of Health of Puerto Rico during 1938, 10.3 percent had posi-

tive tests. From 2,450 health certificates in health units where blood tests are routinely performed, 10.3 percent recorded positive tests.

Of 7,543 agricultural workers of the U. S. Forestry Service in Puerto Rico and the Puerto Rico Reconstruction Administration, 5.7 percent had positive tests. Of 12,403 persons visiting rural medical dispensaries of the Puerto Rico Reconstruction Administration, 7 percent had positive tests.

Among 32,536 selected cases from institutions, hospitals, penitentiaries, and other sources the percent of positive tests varied from 4.1 to 24.9. The lowest percentage (4.1) was obtained from the Boys' and Girls' Charity School. The highest (24.9 percent) was from jails and the insular penitentiary. Other percentages were 19.7 for admittances of males under 30 in a private hospital, 14.2 for four tuberculosis hospitals, and 7.3 for patients admitted to the Psychiatry Hospital at Rio Piedras.

The author concludes that the percentage of possible positive blood tests for the entire population of Puerto Rico is probably between 5 and 6 percent. For urban areas, the figure is probably about 10 percent, for rural areas, about 5 percent. In the larger urban centers the percent of positive results might be slightly higher.

The data are presented in 18 tables and 7 graphs and charts.

The author points out that positive complement fixation or flocculation tests in different groups of the population do not constitute a true or infallible index of the incidence of syphilis in a community. There are some cases of early and late syphilis in which serologic tests are negative. There are cases of yaws, infectious mononucleosis, etc., in which tests may be positive in the absence of syphilis. All of these factors must be considered in interpreting the results of a serologic test survey.

Great increase in number of persons under treatment for syphilis is reported. L. C. Gonzales. Florida Health Notes, Jacksonville, 33: 20-24, Feb. 1941.

Ever since the organization of the Division of Venereal Disease Control in Florida in July 1938, the duties and activities have gradually increased to such an extent that available physical facilities are not adequate. The data show that there has been a marked improvement in the reporting of syphilis, though this cannot be said concerning gonorrhea. The increased number of cases of syphilis in the State is to be interpreted as an indication that unrecognized cases are discovered and that physicians and clinics are reporting more effectively. In 1939, 53.1 percent of the syphilis cases were reported by clinics and institutions and in 1940, 64 percent; 60.1 percent and 39.1 percent of the cases of gonorrhea were so reported for these years, respectively. In 1937 there were only 7 clinics in the State, the monthly average of patients under treatment being reported was 423. In 1938 there were 42 clinics, with 6,693 patients and in 1940, 87 clinics with the monthly average of 8,843 patients. Since approximately one-half to one-third of the reports were sent in from private physicians, it can be conservatively assumed that these figures represent one-half the monthly average of old and new patients under treatment.

In 1940, 258,918 antisyphilitic treatments were given and 342,650 blood specimens examined, each specimen receiving 2 tests. Full-time public health service has been installed in 23 counties. In these counties, as well as in those where there is not full-time service, private physicians are provided with free drugs and laboratory service for the treatment of those patients who are unable to pay for treatment.

The Toxic Dose of Mapharsen Given by the Continuous Drip Method

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THE MASSIVE arsenotherapy of early syphilis by the continuous drip method as proposed at a recent conference on the subject called by the Commissioner of Health of New York City (1) has indicated the serious need for work on experimental animals to determine the maximum tolerated and minimum lethal doses of mapharsen (the hemialcoholate of meta-amino-para-hydroxy phenylarsine oxide) when given by the continuous drip method. Such work is fundamental in the evaluation of any new therapeutic measure and this work to our knowledge has not as yet been done. The present study is concerned with the determination of the maximum tolerated dose and minimum lethal dose of mapharsen given to dogs by continuous drip.

In a previous study (2) we administered mapharsen to dogs in dosages comparable to those proposed for human beings, i. e., 4 mg. per kg. body weight per day for a 5-day period, and found that there was no significant prolonged retention of arsenic and no histologic evidence of damage to the tissues at that dosage level. The excretion of arsenic by these animals was nearly identical to that reported in patients (1). This fact together with the absence of any histologic evidence of damage has led us to feel that the sedative doses of sodium pentobarbital which we have used as an anesthetic in these animals have not seriously interfered with the results.

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Dogs in good health and weighing 10 kilograms or more were used for these experiments. During the experimental period and for at least 3 days before, the animals were kept on a diet of dog biscuit which was high in carbohydrate and protein but low in fat. The animals were fed this diet during the daily 12-hour intervals in which they were not receiving arsenic.

During the actual injection periods the animals were kept quiet by the intravenous injection of minimal required amounts of sodium pentobarbital. At all times anesthesia was kept as light as possible so that the greater portion of the time the animals were drowsy and would lie quietly but retained the eye blinking reflexes. The mapharsen was dissolved in an appropriate amount of 5 percent glucose in distilled water in such concentration that the calculated dosage could be given in 35 to 50 cc. of solution per hour. The injections were given continuously over a 12-hour period without alternating with glucose as was done in the previous study. The injection period was followed by a 12-hour rest and then repeated until the animals had received such treatment during 5 successive days. All injections were made into either the external jugular or the leg veins.

Ten cubic centimeters of venous blood was taken for an arsenic determination before and at the end of each day's treatment. All urine and feces were saved for arsenic determinations. During the injection periods the urine was collected by a retention catheter. Animals which survived the treatment were sacrificed at varying intervals thereafter. Under full sodium pentobarbital

anesthesia they were exsanguinated by severing the abdominal aorta. Specimens for arsenic determination were taken in duplicate wherever the amount of tissue would permit. Tissue specimens were fixed in 10 percent formalin for histologic examination, which was done by Dr. E. M. Hall of the department of pathology.

All arsenic determinations were done by the method of Chaney and Magnuson (3).

RESULTS

The mortality for groups which are designated by the amount of mapharsen administered per kilogram of body weight per day is indicated in table 1. Unless the animal died before the 5-day treatment period was terminated he then received five times this amount as a total dose for the entire period.

TABLE 1.

Dose of mapharsen mg/kg/day	Number animals used	Number animals lived	Number animals died
8	2	2	0
10	4	4	0
12	5	1	4
16	1	0	1

The following is a brief summary of the condition of these animals during and following treatment.

Eight milligrams per kilogram per day. Two animals.—Dog 23, ♂, 12.3 kg. Course was uneventful except for some vomiting during the first day, loss of appetite, and marked tachypnea the fifth day. Maximum rectal temperature was 106.4° F. on fifth day; minimum temperature 98.6° F. on first day. Sacrificed 31 days later. In excellent condition.

Dog 24, ♂, 18.6 kg. Uneventful course throughout save for a mucoid diarrhea on the fifth day. Maximum temperature was 104.6° F. on the fourth day, minimum 93.2° F. on first day. Following treatment became weak and undernourished. When killed 18 days later it was found that he had a perforating posterior duodenal ulcer.

Ten milligrams per kilogram per day. Four animals.—Dog 34, ♂, 11.4 kg. Watery, mucoid diarrhea developed during the second day only. On the fifth day became ataxic and belligerent from which he recovered 2 days later. Maximum temperature was 105° F. on the first day; minimum 94.8° F. on the second day. Sacrificed 9 days later. No abnormalities noted post mortem.

Dog 29, ♂, 10.0 kg. Hematuria developed on the fifth day: 50 red blood cells, 50 leukocytes per high dry field (uncentrifuged). No casts. Dog was quite lethargic during entire treatment period. Maximum temperature was 104.4° F. on the fourth day; minimum temperature was 94.3° F. on first day. Sacrificed 31 days later at which time no abnormalities were noted post mortem.

Dog 30, ♂, 13.6 kg. Had a mucoid diarrhea from second day on. Salivation but no vomiting was noted the first day. Hematuria developed on the fourth day. 50 red blood cells per high dry field of uncentrifuged specimen; 3 to 5 leukocytes per high dry field. No casts or bacteria. Quite lethargic with but little appetite during last 2 days. Maximum temperature 103.3° F. on the third day; minimum temperature 96.8° F. on the third day. Dog was sacrificed 10 days later and no gross abnormalities were noted post mortem.

Dog 28, ♂, 26.4 kg. Entire course was uneventful except for diarrhea during the fourth day. Maximum temperature 101.3° F. on the fifth day; minimum temperature 95.0° F. on the first day. Sacrificed 24 days later at which time no significant abnormalities were noted.

Twelve milligrams per kilogram per day. Five animals.—Dog 31, 13.2 kg. Was lethargic from second day onward. Hematuria developed on the second day which increased in severity during the treatment period. Uncentrifuged urine specimen contained 30 red blood cells and an occasional leukocyte per high dry field but no casts or bacteria. Course otherwise was uneventful. Maximum temperature 102.8° F. on fifth day; mini

imum temperature 93.2° F. on the first day. Sacrificed 17 days later at which time no gross abnormalities were noted.

Dog 32, ♂, 15.9 kg. Pulmonary edema developed during the first and second days. Was almost stuporous throughout the entire course. Severe diarrhea developed the second day which persisted. Hematuria developed the fourth day: 150 red blood cells, 25 leukocytes per high dry field, and 1 to 2 red cell casts per low power field were present in the uncentrifuged specimen. Vomited several times during the fifth day and died about 3 hours after treatment was finished. Maximum temperature was 104.4° F. on the second day; minimum temperature 96.8° F. on the fifth day. At post mortem examination the lungs were edematous, and all the tissues were congested. The liver was of a peculiar red-orange color.

Dog 33, ♂, 12.7 kg. Vomited several times during the second day. Hematuria developed the second day; uncentrifuged urine contained 50 red blood cells per high dry field. Died during night between second and third days. Maximum temperature was 101.8° F. the second day; minimum temperature 93° F. the first day. All tissues were markedly congested at post mortem examination.

Dog 25, ♂, 10.0 kg. Diarrhea developed at the end of the first day. Somewhat toxic second morning. Died during night following second day. Maximum temperature 102.6° F. first day; minimum temperature 89.6° F. second day. During entire second day appeared to be in severe shock. At autopsy tissues were all congested, but no other gross abnormalities were noted.

Dog 27, ♀, 22.7 kg. Was almost comatose the second morning. During the second day began to bleed from gums and rectum. At the end of the second day the bleeding time was in excess of 45 minutes. Blood drawn into test tube failed to clot even after 3 days. Blood count was 6,270,000 red cells, 1,450 leukocytes, and 20,000 platelets per cubic millimeter. Differential count of a stained smear revealed 82 percent polynuclear neutrophils, 16 percent lymphocytes, and

2 percent monocytes. Prothrombin time was not obtained. On the third morning the dog was comatose. Following a massive hemorrhage from the rectum she died a respiratory death, having received one hour's injection. At autopsy the mucous membranes were very cyanotic, and there was extreme congestion of the right ventricle, auricle, and superior and inferior vena cava. Subendocardial hemorrhages were present in both ventricles. The liver was friable, mushy, and necrotic. Blood did not clot post mortem.

Sixteen milligrams per kilogram day.
One animal.—**Dog 26, ♀, 14.1 kg.** Pulmonary edema developed which became progressively more severe during the first day. On the second morning was unable to stand. Diarrhea had developed. Died during the night following the second day. Animal appeared to be in severe shock during both days. Maximum temperature was 93.7° F. the first day; minimum temperature was 87.8° F. the second day. At autopsy the only remarkable change noted was extensive congestion of all the tissues.

The above data would indicate that the maximum tolerated dose of mapharsen given by continuous drip is approximately 10 mg. per kg. of body weight per day for a 5-day period and that the minimum lethal dose is 12 mg. per kg. of body weight for same period.

It is of interest to consider the mortality rate in relation to the excretion of arsenic by these animals. Was dog 31 able to survive 12 mg. per kg. of body weight per day because he was able to excrete more arsenic than the other animals which received 12 mg. per kg. of body weight per day?

In order to ascertain this, the sum of the urinary and fecal excretions during the 5-day period was determined. That which was not excreted by the above channels was assumed to be retained, though such an assumption introduces some error through the lag in fecal excretion. The percentage retained was multiplied by the amount of mapharsen given in mg. per kg. of body weight per day to determine the amount of

mapharsen retained in mg. per kg. of body weight per day. The results arranged in order of the amounts retained are given in table 2.

TABLE 2.

Amount mapharsen given mg/kg/day	Dog No.	Mg. mapharsen/kg/day retained	Fate
8	23	4.5	Lived.
10	34	4.8	Do.
8	24	4.9	Do.
10	29	5.1	Do.
10	30	5.5	Do.
10	28	5.7	Do.
12	31	6.0	Do.
12	32	7.0	Died sixth day.
12	33	8.4	Died third day.
12	25	8.5	Do.
12	27	9.6	Do.
16	26	10.5	Do.

From the above it may be seen that there was a direct relationship between amount of arsenic retained and the fate of the animal. However, it may be argued that most of the animals who died did so at the end of 2 days of treatment so that comparison should be made on the basis of the amounts excreted during the first 2 days only, regardless of whether the animal lived 5 or more days. This was done with the following result (table 3), again arranging the animals in the order of increasing amounts of arsenic retained.

TABLE 3.

Amount mapharsen given mg/kg/day	Dog No.	Mg. mapharsen/kg/day retained (first 2 days only)	Fate
10	34	3.9	Lived.
8	23	5.5	Do.
12	31	6.2	Do.
8	24	6.3	Do.
10	29	6.35	Do.
10	30	6.9	Do.
10	28	7.6	Do.
12	32	8.0	Died sixth day.
12	33	8.4	Died third day.
12	25	8.5	Do.
12	27	9.6	Do.
16	26	10.5	Do.

On this basis it may be seen that the animal which received 12 mg. per kg. of body weight per day and lived retained

less arsenic during the first 2 days than one of the animals which received 8 mg. per kg. per day. We have not as yet encountered the situation in which a dog receiving 10 mg. per kg. per day died because he did not excrete the drug at a sufficiently rapid rate, though it seems reasonable to anticipate such a situation.

One must be cautious in assuming that the animals died as a result of failure to excrete the arsenic. From the evidence presented it is not certain whether the failure of excretion was primary and led to tissue damage with death of the animal, or whether the failure of excretion was a result of tissue damage which later resulted in death of the animal. The most that one can say is that there was a direct relation between the amount of arsenic excreted and the fate of the animal.

The concentrations of arsenic in whole blood expressed as micrograms of arsenic per hundred cc. of blood are indicated in figure 1. The numbers along the abscissa refer to the days of treatment and the letters "a" and "p" refer to the morning and evening levels respectively. The difference between concentrations found in the animals who received 12 mg. per kg. per day and those who received 10 mg. per kg. per day is striking, the slope of the former curve being much steeper both for the maximum and minimum values. It is apparent that arsenic is not excreted at a sufficiently rapid rate to maintain the blood levels at lower values. It may also be said that there is no one certain level of concentration of arsenic in the blood at which death of the animal occurs, so that while the blood arsenic level may indicate the general course, it cannot serve as a basis for predicting with certainty the fate of the animal.

The results of arsenic determinations on the tissues obtained at the time of death or of sacrifice of the animal are recorded in table 4. The results are expressed in micrograms of arsenic per 100 mg. of wet tissue except in the case of bile. The figure for the bile represents the amount of arsenic found in all of the bile obtained from the gall bladder.

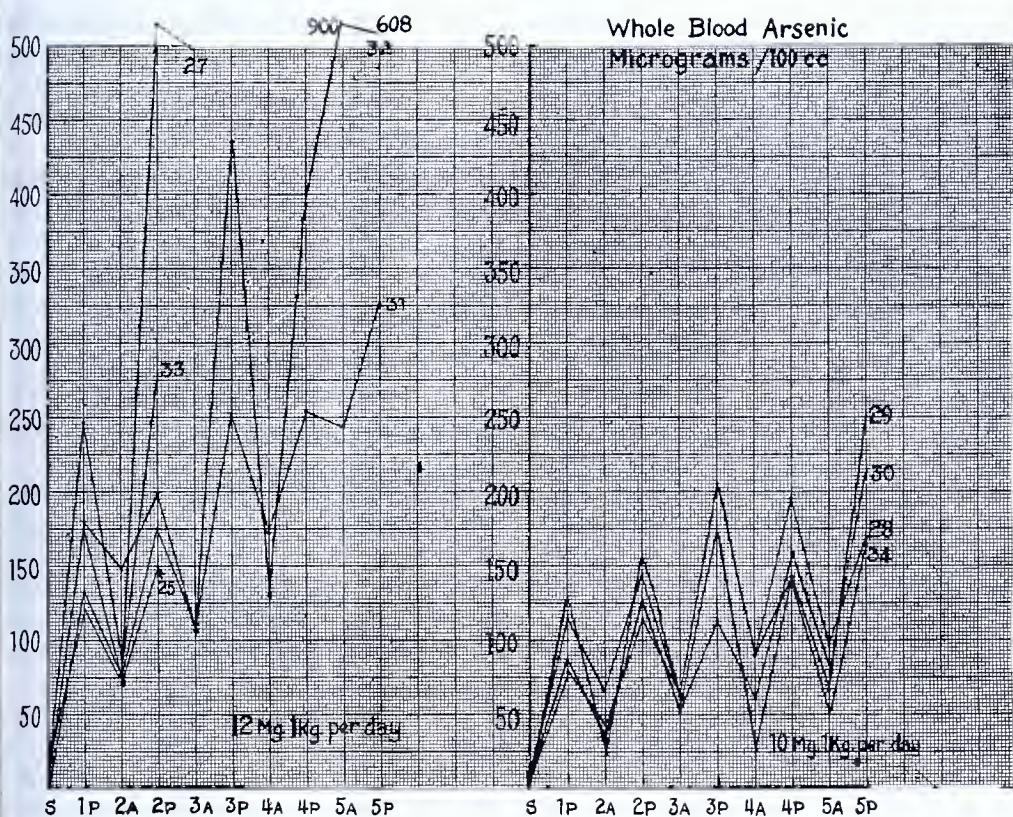


FIGURE 1.

TABLE 4.

	8mg/kg/day		10 mg/kg/day				12 mg/kg/day				16mg/kg/day	
Animal No.-----	24	34	30	28	29	25	33	27	32	31	26	
Days treated-----	5	5	5	5	5	5	2	2	5	5	2	
Days following treatment-----	18	9	10	24	31					17		
Heart-----	15	12	6	7	59	74	200	250	330	7	120	
Lung-----	17	25	5	10	27	150	325	860	460	12	390	
Bile-----	3	1	0	.25	.8	146		580		0	1,134	
Liver-----	23	53	30	31	16	960	1,500	1,900	920	44	1,500	
Spleen-----	20	66	60	36	17	207	570	855	450	135	266	
Kidney-----	38	113	75	9	20	450	900	1,480	1,120	52	1,234	
Pancreas-----	11	16	10	1	15	95	190	380	417	13	140	
Testicle-----	7	11	15		8	42	142		185	10		
Skeletal muscle-----	8	15	14	0	6	91	260	265	344	17	122	
Thyroid-----	5	16		3	33	116		840	536	46	273	
Peripheral nerve-----	44	0	24	41	70	82		174	398	21		
Aorta-----	5	9		3	11	174		449	500	15	236	
Brain-----	6	11		12	15	17	75	30		22	67	
Bone-----	10	11	11	10	86	36	200	200	107	85	46	

The concentrations of arsenic found in the tissues of the animals that died during treatment are, of course, extremely high. Comparing the results obtained from this group of animals with those from our previous group which received 10 mg. per kg. of body weight per day it is seen that there is a trend toward a

somewhat longer retention of the arsenic, especially in the spleen. One may speculate as to whether or not this is a result of more tissue damage in the animals which received higher dosages.

In this group of animals the concentrations of arsenic in bones were definitely lower than those found in the

previous group. Whether this is because of a slightly different diet, different dosage, or just individual differences in animals, we do not know.

Microscopic examination of the tissues obtained revealed the following changes.

Eight milligrams per kilogram per day.—Dog 23. Liver: The liver cells appear swollen, obliterating partially the usual trabecular arrangement. In many of the cells around the portal spaces and in the peripheries of the lobules there is marked granular swelling. There is no necrosis.

Kidney: There is considerable granular swelling of the tubular epithelium and moderate congestion. Lipoid stains show patches of fatty metamorphosis mainly in the collecting tubules, principally in the ascending loops of Henle.

Brain: The meninges are congested. There is an occasional tiny hemorrhage in the cortex and a few red cells are seen in the Virchow-Robin spaces about a few of the vessels.

Lung: The alveoli are practically all clear. There is slight thickening of the septa in a few areas. The smooth muscle in the walls of the bronchioles appears to be definitely hypertrophied. There is some hyperplasia of the bronchiole epithelium in some of the larger bronchi.

Heart: Lipoid stain of the heart muscle shows accumulation of fat about many of the vessels.

Spleen: The capsule appears somewhat thickened. The trabeculae are very prominent, and some of them are quite broad. The pulp is definitely atrophied. There is considerable increase in dark brown hematogenous pigment. The lymphoid tissue is fairly abundant.

Dog 24. Liver: Liver cells are distinctly swollen in the peripheries of the lobules. This involves about half of each lobule. Sudan III stain showed no increase in lipoid.

Kidney: There is granular swelling of the tubular epithelium. This is most marked in the collecting tubules. The glomeruli appear to be normal. There is no increase in lipoid.

Brain: There is fairly well marked congestion of the meninges and of the brain substance. A small area of softening about 1 mm. in diameter is seen in one place only.

Lung: There is considerable thickening of the septa. Many of the alveoli are obliterated, and many of those remaining are dilated and emphysematous. There are many large mononuclear cells in the thickened septa. This seems to be a chronic interstitial pneumonia.

Heart: The fibers appear crowded with very slight hemorrhage here and there. There is no increase in lipoid.

Spleen: The trabeculae are prominent and there is atrophy of the pulp. Lymphoid tissue is fairly abundant. There is only slight congestion. There seems to be an increase in the large mononuclear cells in the splenic pulp.

Pancreas: Normal.

Ten milligrams per kilogram per day.—Dog 34. Liver: Cells are very pale staining throughout with vacuolization of cytoplasm, no doubt due to dissolving out of glycogen.

Kidney: There is parenchymatous degeneration of the tubular epithelium with no other abnormalities.

Brain: Moderate congestion of the meninges and moderate edema of the brain substance are present.

Lung: Normal.

Heart: Normal.

Pancreas: Normal.

Dog 29. Liver: The cells stain poorly. This is especially true of the centers of the lobules. There is a fine vacuolization of the cytoplasm in these areas. Sudan III stain shows some very fine lipoid material resembling lipochrome. This is seen more abundantly in the pale cells around the centers.

Kidney: There is only granular swelling of the tubular epithelium. No lipoid is seen.

Brain: There is moderate congestion in the meninges and only slight congestion of the brain substance. A few of the small vessels show red cells in the Virchow-Robin spaces. Some of the nerve cells take a dark purplish stain.

and fail to show little, if any, tigroid substance.

Lung: Normal.

Heart: Muscle stains rather poorly. No lesions can be made out. Sudan III stain shows globules of fat about the vessels and between some of the muscle bundles.

Spleen: The trabeculae are prominent and lymphoid tissue is fairly abundant. A moderate amount of fine brown pigment is present in the pulp.

Pancreas: Normal.

Dog 30. Liver: Liver cells are pale staining and are finely vacuolated throughout. This appears to be due to absence of glycogen. Some lipochrome is seen on fat stains.

Kidney: There is fairly heavy infiltration about some of the vessels. There is rather marked granular swelling of the tubular epithelium, especially the collecting tubules. Sudan III stain reveals a patchy, fatty degeneration of the epithelium of the collecting tubules, apparently in the ascending loops of Henle.

Brain: The meninges are markedly congested. The brain substance is moderately so. The spaces are rather large about the vessels, probably indicating edema.

Lung: The lung shows more or less collapse with thickening of the septa. Many of the vessels are engorged. There is hyperemia of the septal capillaries.

Heart: Normal.

Spleen: There is increase in the amount of dark brown pigment; otherwise normal.

Dog 28. Liver: The cells stain poorly and many of the cells are vacuolated. This is probably due to dissolving out of glycogen. No areas of necrosis were seen. There is increased lipochrome pigment about the centers of the lobules.

Kidney: There is rather marked congestion. The glomeruli appear to be normal. There is granular swelling of the tubular epithelium. Another section of kidney shows more or less coagulated fluid in the spaces of Bowman. There is fairly

marked granular swelling of the epithelium.

Brain: There is moderate congestion of the meninges of the brain substance. Two or three vessels show hemorrhage into the surrounding Virchow-Robin spaces. There are no areas of softening.

Lung: There is thickening of the septa in many places. The alveoli are clear. There is a considerable amount of dark brown pigment about many of the bronchi.

Heart: The muscle stains palely. There is an occasional small capillary hemorrhage. Sudan III stain shows no abnormalities.

Spleen: The capsule is thick with prominent trabeculae. There is moderate atrophy of the pulp. Lymphoid tissue is fairly abundant. There is moderate increase in finely granular dark brown pigment.

Twelve milligrams per kilogram per day.—Dog 31. Liver: Cells are pale staining and much of the cytoplasm is finely vacuolated. There is engorgement of many of the vessels. Liver cells appear somewhat crowded. Some lipochrome granules are seen about the centers.

Kidney: There is rather marked granular swelling in the tubular epithelium but no lipid. There is slight round cell infiltration about some of the vessels.

Brain: There is only slight congestion of the meninges. Some of the vessels of the brain substance are moderately engorged. There is moderate edema.

Lung: There is partial collapse. The muscle about the bronchioles is definitely hypertrophied. The vessels are moderately engorged.

Heart: There are one or two small hemorrhages and some perivascular infiltration of fat.

Spleen: There is considerable increase in dark brown hematogenous pigment. The pulp appears atrophic. The lymphoid tissue is reduced in amount.

Pancreas: The groups of islet cells are very small.

Dog 32. Kidney: There is marked congestion with engorgement of the vessels. The glomeruli also are hyperemic. There is marked granular swelling of the tubular epithelium with early necrosis. There is some interstitial hemorrhage among the tubules.

Brain: The meninges are moderately congested. There is marked congestion of the brain substance. The red cells are spread over into the Virchow-Robin spaces in a few places.

Lung: Small groups of alveoli here and there contain coagulated fluid and a moderate number of polymorphonuclears. A number of the bronchi are filled with purulent exudate. Many of the vessels are engorged. The septa are thickened in many places. *Another section of lung* shows a large number of alveoli filled with coagulated fluid and polymorphonuclears. All of the bronchi are filled with purulent exudate. Bronchopneumonia.

Heart: There is considerable thickening of the walls of some of the larger vessels, mainly medial. The vessels are engorged with blood. The muscle is pale staining. Fat stains show a perivascular fatty infiltration of the heart.

Spleen: There is moderate congestion. There is slight increase in brown pigment.

Small intestine: There is moderate hypertrophy of the muscle but no other abnormalities.

Dog 33. Liver: There is intense and diffuse congestion. Practically all of the sinusoids are dilated and filled with blood. No areas of necrosis are seen. There is some increase in lipochrome.

Kidney: Marked congestion is present. The glomeruli are essentially normal. There is granular swelling of the tubular epithelium. There is round cell infiltration about a few of the vessels.

Brain: There is marked congestion of the brain substance and some edema.

Lung: Marked congestion is present throughout. Many leukocytes and red blood cells are in the alveoli, also more or less coagulated fluid. *Another section of lung* shows marked congestion with some hemorrhage into the alveoli in places.

Heart: There is hemorrhage around an occasional vessel and several small areas of interstitial hemorrhage. A perivascular infiltration with fat is noted in sections stained with sudan III.

Spleen: There is apparent atrophy and a considerable increase in brown hematogenous pigment.

Small bowel: Normal.

Dog 25. Liver: The portal veins are greatly engorged with blood, and in some portions, especially the subcapsular, the sinusoids are distended with blood. Some parts of this region present evidences of early necrosis. In other parts the liver cells contain small vacuoles, probably the result of fatty degeneration. The nuclei stain fairly well. In some regions the sinusoids contain many red cells which are devoid of hemoglobin.

Kidney: The glomeruli are extremely congested but otherwise appear to be normal. The vessels of the interstitial tissue are all engorged with blood. Early necrosis is seen in the cells of the tubules, especially in the ascending loops of Henle. Many of the epithelial cells in the collecting tubules contain fine vacuoles. No blood nor casts are seen within the tubules. The epithelium is markedly swollen in many places. The interstitial tissue is definitely edematous.

Brain: The vessels of the pia are extensively engorged and the brain tissue itself presents a considerable amount of congestion. Slight hemorrhages into the Virchow-Robin spaces are seen, at least in some portions.

Lung: Many small areas are seen in which the alveoli are filled with blood, many of them apparently are collapsed, and some are filled with coagulated fluid. The larger vessels are engorged with blood, but there is no pneumonic consolidation.

Small intestine: In many sections the epithelium over the tips of the villi is desquamated and there is slight round-cell infiltration in this portion. The mucosa is moderately congested but otherwise the wall is normal.

Dog 27. Kidney: Aside from the congestion of the glomeruli and engorgement

of the large vessels, no abnormal changes are evident. The conditions are similar to those described in other specimens.

Brain: Congestion and recent hemorrhage are present in the pia. The large nerve cells are pale, stain very poorly, and there is no stainable tigroid material. In some instances the nuclei cannot be seen.

Lung: The septa are markedly congested; the larger vessels engorged and many of the alveoli are filled with coagulated fluid. The bronchi are clear and there are no areas of consolidation.

Dog 26. Liver: An extreme degree of congestion is seen throughout, and the larger vessels are engorged. In some portions the liver cell trabeculae are more or less disorganized. In many portions there is evidence of early necrosis but no infiltration of the polymorphonuclear leukocytes.

Kidney: Aside from a rather marked degree of congestion, the glomeruli are normal. The epithelium of the tubules presents definite evidence of granular swelling and here the nuclei are rather pale but can be made out in practically all portions. In the interstitial tissue a considerable degree of edema and engorgement of the large vessels is present.

Brain: Aside from moderate congestion of the meninges and perivascular hemorrhage in the region of one or two vessels the tissue appears to be normal.

Lung: Many alveoli contain coagulated fluid, debris, and fibrin. Marked congestion and engorgement of the vessels are seen in the septa. In the tissue about some of the bronchi, regions of pneumonic consolidation are present, and many of the bronchi are filled with desquamated epithelium and small masses of fibrin. There are no polymorphonuclear leukocytes.

Spleen: Many of the venous spaces contain masses of cellular material in the form of whorls. They have a granulomatous appearance. Lymphoid tissue is greatly reduced in amount.

Small intestine: The mucous membrane appears to be hypertrophic and a moderate degree of desquamation of

epithelium is seen over the tips of the villi. Aside from this and moderate congestion, the intestine is normal.

COMMENT

Tatum and Cooper (4) in their original work on mapharsen found that with single injections the M. L. D. for dogs was 15 mg. per kg. of body weight and the M. T. D. was 12 mg. per kg. of body weight. Our results would indicate that by continuous drip the M. L. D. is 12 mg. per kg. of body weight per day for the 5-day period and the M. T. D. is approximately 10 mg. per kg. of body weight per day for the same period.

Thus in a 5-day period one may administer 50 mg. per kg. of body weight and still not exceed the M. T. D. That this is greater than could be given in a single dose is obvious, but whether it is more than could be given by multiple divided doses without the continuous drip is yet to be determined. That the tolerance would be found to be increased by divided doses over the single dose is suggested by the statement of Tatum and Cooper that they were able to give dogs 8 mg. per kilogram three times a day at 4-hour intervals without any serious symptoms of toxicity.

Our experiences regarding the death of the animals was similar to those of the above authors who found that fatal doses always killed the animals within the first 24-hour period. We had no deaths which did not occur either during the course of treatment or immediately following. The animals which survived appeared to be normal within 1 to 2 days after cessation of treatment except that a few continued to have diarrhea.

Attention should be called to the fact that animals which survived the treatment and appeared grossly normal at autopsy presented varying degrees of microscopic damage to the tissues. These changes were not encountered in the previous series in which four milligrams per kilogram of body weight per day was administered.

With the exception of dog 27 those animals that died apparently did so because

of severe diffuse capillary damage, such as one would expect in acute arsenic poisoning. The picture resembled that of severe shock with subnormal temperature, cold extremities, very slow venous filling in the extremities so that it was difficult to obtain blood, varying degrees of lethargy, and finally coma. At autopsy the most striking single change was the extreme congestion of all the tissues, both grossly and microscopically.

Dog 27 was particularly interesting because of the bleeding which developed. The blood clotted normally before treatment was begun, though no counts of the red cells, white cells, or platelets were made before the experiment was started. Even though the platelets were depressed it appears improbable that the bleeding could be accounted for on that basis alone, and it is probable that the severe liver damage played a major role in production of the hemorrhage. It is unfortunate that we were not able to obtain a prothrombin time.

The hematuria which developed in so many of the animals came on in such manner as to indicate that trauma due to catheterization was not responsible. The onset was insidious and once the hematuria had begun it became progressively more severe. In one instance red blood cell casts were noted.

A comparison of the therapeutic index obtained by the continuous drip versus single injection must await experiments on rabbits. Some interesting comparisons may be made, however, on the data now available. Thus the generally accepted weekly dose of mapharsen given in conventional therapy approximated 1 mg. per kg. of body weight while the M. T. D. in dogs by single injection is 12 mg. per kg., giving a ratio of 12. The dose of mapharsen which has been used in the continuous drip treatment of syphilis approximates 4 mg. per kg. per day for a 5-day period, while the M. T. D. in dogs by the continuous drip is 10 mg. per kg. per day, giving a ratio of 2.5. This would certainly suggest that the margin of safety is considerably less and that much caution must be used in accepting the continuous

drip as a general form of therapy. That the margin of safety is less is further indicated by the one-percent incidence of central nervous system complications encountered by the New York group in their patients who were treated with mapharsen.

CONCLUSIONS

1. The maximum tolerated dose of mapharsen when given to dogs by the continuous drip method for a period of 5 consecutive days is 10 milligrams per kilogram of body weight per day.
2. The minimum lethal dose for the same conditions is 12 mg. per kg. per day.
3. The M. T. D. and M. L. D. are such as to indicate the need for considerable caution in the administration of massive doses of mapharsen to patients by the continuous drip method.

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Evaluating a Serologic Test for Syphilis in a Metropolitan Community¹

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and

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IN KEEPING with the present attempt to stamp out syphilis in this country, the St. Louis Health Division in cooperation with the United States Public Health Service and the Missouri State Board of Health inaugurated a new venereal disease control program in 1939. Evaluating the serologic test for syphilis in the St. Louis laboratories became the task of the health division laboratory. Questionnaires submitted to all St. Louis medical institutions disclosed that 33 out of 42 conducted serologic tests for syphilis and that 26 (80 percent) of the 33 performed the Kahn test. This was the principle reason for adopting this test as the standard serologic procedure in St. Louis. The health division's 13 years' experience with the Kahn test also influenced the decision.

Surveys were conducted in the 26 institutions doing the Kahn test and in the remaining 7 after this test had been adopted. A member of the health division laboratory observed the performance of the test and inspected the equipment in the various laboratories. An outline containing pertinent information regarding equipment, reagents, and technique based upon Dr. Kahn's latest publications² was used as a guide. Each laboratory was required to use a Kahn mechanical shaker, thermostatically controlled water bath, and standard glassware. The technicians were invited to the health division laboratory to check their reading ability. If the facilities were found to be inadequate, and if the technic deviated from that prescribed by

Kahn, a written recommendation was submitted to the laboratory.

Improper reading of the test was the most conspicuous cause of variation in results. Figure 1 shows that reading was done incorrectly in 17 laboratories. The greatest number of these laboratories missed positive and doubtful reactions because they were not using the proper light arrangement, others because of improper interpretation of the amount of precipitate present or because of dirty or badly scratched glassware. Daylight was utilized in all but two laboratories, and in 3 laboratories a 10-X microscope eye piece was used.

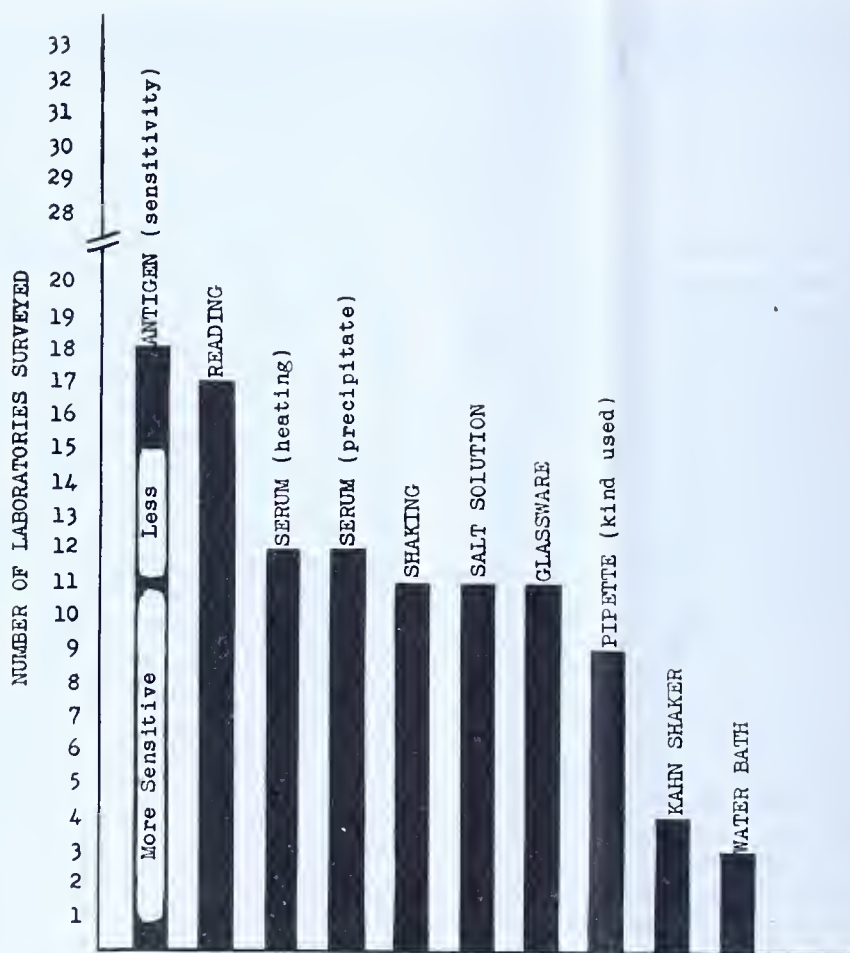
The antigen used in the Kahn test also was an important factor in causing discrepancies in some laboratories. Of 28 samples of antigen which were compared with standard antigen secured from Dr. Kahn, 11 were found to be more sensitive, 4 were less sensitive, and 3 contained a large amount of precipitate. In three institutions the standard antigen was kept in the refrigerator, and in two instances a partially dissolved rubber stopper was used in the antigen bottle. Many of the containers in which antigen was kept were closed with loosely fitting stoppers.

Blood specimens were not centrifuged properly in 12 laboratories. In a few instances negative serums were probably being reported as positive because of the large amount of precipitate found in the specimens.

Water baths were maintained at temperatures anywhere between 54° and 58° C. in 12 laboratories despite the fact that it has been shown that even one degree variation from 56° C. over a period of 30 minutes definitely influences the sensitivity of the test. Three laboratories were not equipped with thermostatically controlled water baths.

¹ From the St. Louis Health Division Laboratory, St. Louis, Mo.

² Kahn, R. L.: The Kahn Test, Baltimore, Williams and Wilkins, 1928; Technics of Serodiagnostic Tests for Syphilis, Supp. No. 11 to Ven. Dis. Inform., U. S. Public Health Service, 1940.



LABORATORIES DEVIATING FROM STANDARD KAHN PROCEDURE

FIGURE 1.

The salt solution presented another problem. In two or three instances the amount of extraneous material present was sufficient to make negative tests look like positive tests. Many technicians failed to shake the test properly. Four laboratories were not equipped with mechanical shakers. Tubes of all sizes and descriptions were used in 11 laboratories.

One point of technic which has a direct bearing on the accuracy of the Kahn test is the size of the pipette used in measuring small amounts of reagents. Nine laboratories were using either 5 or 10 cc. pipettes for measuring 1 or 2 cc. of antigen and salt solution in making the emulsion.

After all laboratories had acquired standard equipment and after the technician had shown sufficient ability to conduct and read the Kahn test, the health

division furnished Kahn antigen to each laboratory. This antigen was made in the health division laboratory and was checked and approved by Dr. Kahn. The laboratories were then divided into small groups of 6 to 8 each and were checked with split identical specimens procured by the health division venereal disease service. Each laboratory received about 10 specimens 3 days a week until 70 to 120 specimens were examined. In order to evaluate the results obtained by the respective laboratories, the findings reported by the majority were considered as the correct Kahn report.

Figure 2 shows the percent deviation (absolute and relative) obtained by 31 laboratories when compared with the correct report. Twenty laboratories obtained satisfactory results in one series

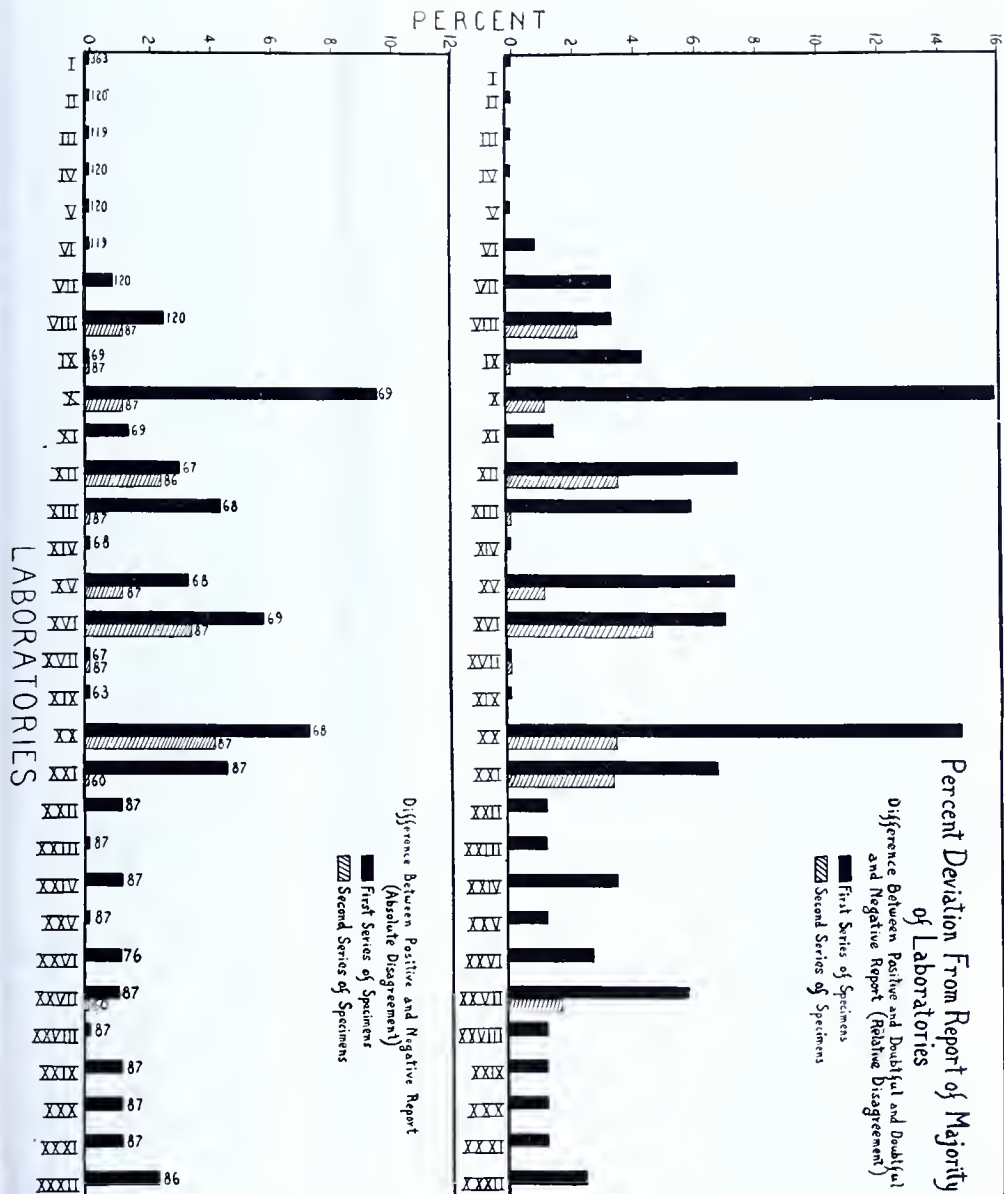


FIGURE 2.

of check specimens in that they showed only 0 to 2 percent absolute deviation from the correct report, while nine failed to agree with the correct report on 3 to 10 percent of the specimens examined in the first series. In analyzing the deviations from the correct report, one plus differences were not considered important and hence were not included in the analysis.

The laboratories that failed to agree with the majority report returned the technicians to the health division laboratory for additional instructions. A sec-

ond series of check specimens was then sent to these laboratories. Figure 2 shows also the improvement obtained with this series of specimens. Laboratory X, for example, showed remarkable improvement since the percentage error decreased from 10 to 1. All laboratories (except XVI) showed satisfactory results after the second series of specimens. Laboratory XVI checked a third series of 30 specimens and obtained complete agreement with the health division laboratory.

Before final approval of the respective laboratories, a number of carefully se-

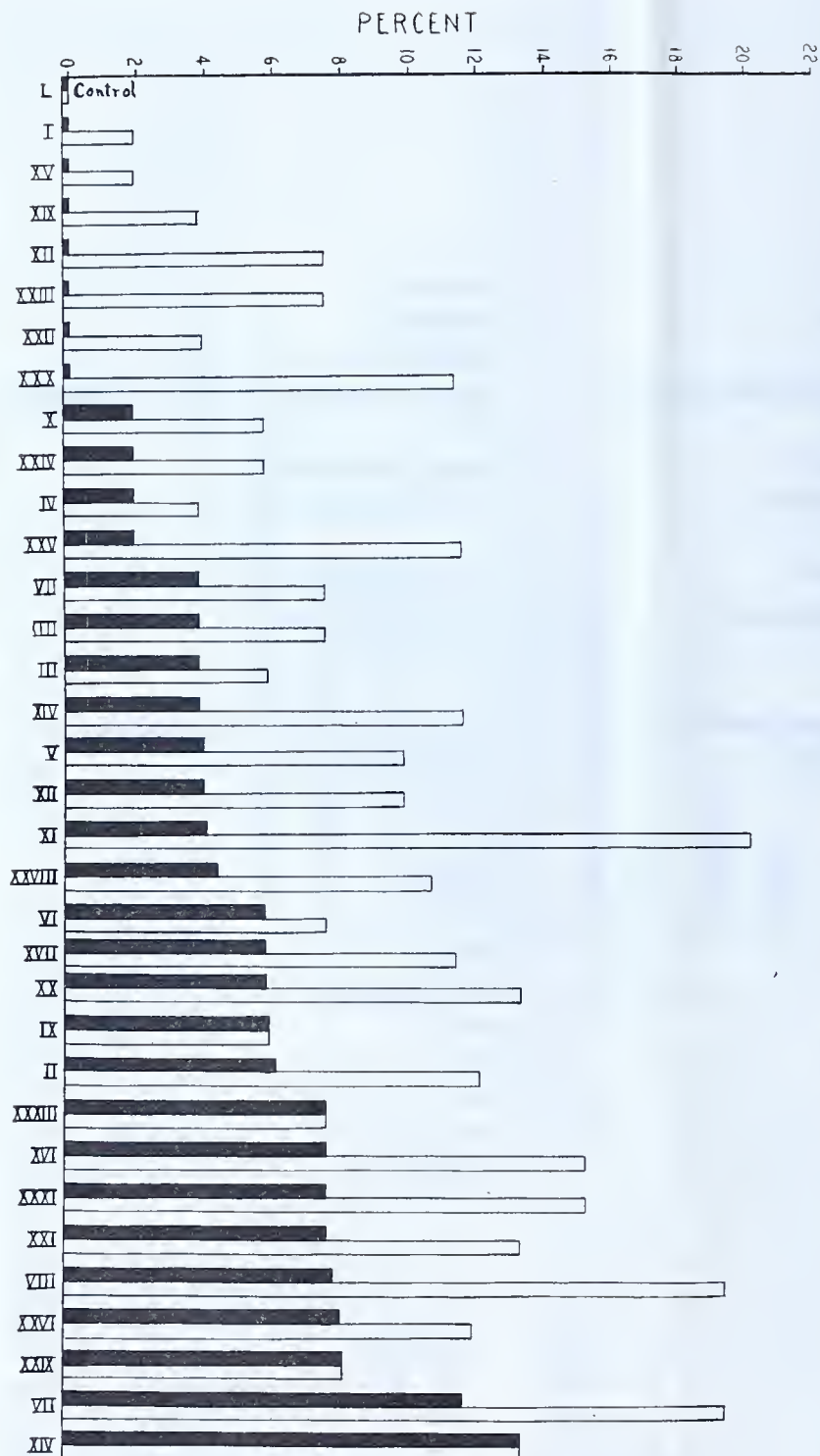


FIGURE 3.

lected split identical serums were sent to each of the 33 laboratories and to Dr. Kahn's laboratory, which served as control. This group of specimens consisted of 15 negative reacting serums, 6 + + + +,

6 + + +, 16 + +, and 10 + serums. Seven of the 15 negative serums were procured from syphilitic individuals who had had recent doubtful reactions.

As shown in figure 3, 31 of the labora-

ories did not deviate more than 8 percent in significant results from those reported by the control laboratory. Seven laboratories agreed closely with the control in that no results were obtained showing differences between a positive and negative report. Twelve laboratories showed a 1- to 5-percent absolute deviation, while 12 other laboratories showed 5- to 8-percent difference. Only two laboratories (VII and XIV) showed more than 10 percent absolute deviation.

Table 1 shows how the laboratories agreed on a few representative serums in the final series of 53 specimens. Of the specimens obtained from the group of presumably nonsyphilitic individuals, one (case 41) was reported negative by 2 laboratories and positive (2 plus) by the remaining two laboratories. The re-

sults with serum from case 53 were quite consistent, 31 laboratories reporting the specimen negative and 3 reporting the specimen as doubtful. Some of the results obtained were somewhat less consistent in the weakly positive specimens from the nontreated cases of late latent syphilis. The specimen from case 42, for example, was reported positive (++) in 19 laboratories, +++ in 11 and ++++ in 1 laboratory) by 31 laboratories and negative by 3 laboratories. Similar inconsistencies, although few, were found among specimens obtained from the treated cases of late latent syphilis. Variable results were obtained with the serum from the patient with neurosyphilis (case 28). Twenty laboratories reported this serum negative; 11 reported it doubtful; and 3 reported it positive.

TABLE 1.—Results reported on representative samples of the final series of 53 identical blood specimens submitted to 34 laboratories

Clinical history	Treatment	Case No.	34 laboratories reporting specified serologic reactions						Specimens damaged
			Control ¹	4+	3+	2+	Doubtful	Negative	
Presumably nonsyphilitic		53	Negative				3	30	
		41	do			1	2	30	
		42	do			2		31	
Primary syphilis	Not treated	11	do			2	5	26	
		40	Doubtful	5	7	15	6		
		44	2+		1	5	21	5	1
Early latent syphilis	Treated	54	3+		6	10	13	4	
		54	Doubtful		1	3	20	9	
		42	2+	1	11	18		3	
Late latent syphilis	Not treated	43	4+	22	8	3			
		14	2+		8	16	7	2	
		39	3+	4	17	9		1	2
Congenital syphilis	do	6	2+	7	16	10			
		9	4+	32	1				
		28	2+	1	4	18	8	2	
Neurosyphilis	do		Doubtful		1	2	10	20	

¹ Performed in the laboratory of Dr. Reuben L. Kahn, University of Michigan.

SUMMARY

Although the Kahn test is a comparatively simple procedure it is obvious from the results of this cooperative study that many factors may alter the accuracy of this test. Physical equipment and the quality of the reagents used are of utmost importance. The training and ability of the technician also plays an important role in unifying this or any serologic procedure. The results obtained would indicate that with the use of standard equipment and reagents

and with properly trained technicians it is possible to obtain satisfactory results in the majority of laboratories.

In view of the close cooperation of this group of laboratories toward the attainment of the common objective, that of uniformity in the serologic diagnosis of syphilis, only two (6 percent) of the laboratories showed more than a 10-percent significant deviation from the control laboratory. By our method of appraisal only positive to negative or negative to positive differences from the

control laboratory were considered significant deviations.

In addition, any evaluation study of this kind must be judged in the light of the kind of specimens submitted for checking purposes, since weakly positive reactions obviously will yield more discrepant results.

CONCLUSION

It is evident from results obtained in St. Louis that if comparable results are to be obtained in a group of laboratories using the same serologic test in the laboratory diagnosis of syphilis, the following points must be adhered to:

1. Local, convenient, training facilities must be available for technicians.
2. The technic employed must follow exactly the procedure of the author-serologist, and should be checked by a competent worker.
3. Standard reagents and certain minimum equipment must be available.
4. Periodic checking of the laboratory with properly selected specimens must be made by a control laboratory.

This study was made possible through the initiative and cooperation of Dr. J. F. Bredeck, Health Commissioner, and Dr. F. C. Gillick and staff of the Venereal Disease Service. Thanks are due to Dr. S. E. Sulkin, research bacteriologist, for his valuable aid in analyzing and assembling this data.

DIAGNOSIS

The adequate diagnosis of infantile congenital syphilis. Norman R. Ingraham, Jr., Bertram Shaffer, Barbara E. Spence and James H. Gordon. *Arch. Dermat. & Syph.*, Chicago, 43: 323-340, Feb. 1941.

A 5-year follow-up study of 230 infant offspring of syphilitic mothers born at the Philadelphia General Hospital during 18 months from October 1933 to April 1935 is presented. Approximately one third of the syphilitic group were known

to have died, as compared with one tenth of the nonsyphilitic group, but it was possible to reexamine about 70 percent of the remaining living children after 4 to 5 years.

No infant was discovered in whom serologic tests and the roentgenographic procedures employed had not furnished evidence on which to establish the diagnosis of syphilis in infancy, if it was present. The spontaneous remission of clinical symptoms and the disappearance of laboratory evidence of the disease after comparatively little or, at times, no antisyphilitic treatment was found to be a relatively frequent occurrence among the syphilitic infants who survived the first few months of their disease. Hyperpyrexia from an intercurrent infection may be one of the factors which bring about this apparent "cure." An analysis of infants diagnosed as syphilitic showed that 13 were clinically and serologically cured with no treatment, 12 with inadequate treatment, and 15 with more than a year of active therapy; 10 had died who had received no treatment and after inadequate treatment; 3 inadequately treated and 3 with more than a year's treatment still showed symptoms of syphilis.

To determine the practical importance of recent advances in serologic and roentgenographic diagnosis of infantile congenital syphilis the authors have compared results in the 5-year study with those obtained in 16 months from September 1938 to January 1940. Misinterpretation of the roentgenogram of the long bones, which introduced errors as great as 12 percent 5 years ago, is becoming uncommon, largely through better understanding of (a) the occurrence of rather wide variations in normal metaphyseal densities, (b) the effect of prepartal treatment of the mother, with heavy metals in producing opaque shadows in the shafts of the infant bones, and (c) the importance of differentiating the early osteochondritis from periosteal changes developing in the malnourished rachitic infant 2 to 4 months of age. Other causes of diag-

diagnostic error have been infrequent in the authors' experience. Significant roentgenographic changes as a result of syphilis in an infant with negative serologic reactions of the blood are likewise unusual. It is believed that the use of the roentgenogram as a subsidiary diagnostic aid will be found of greatest value in those cases in which a recent infection of the mother or grossly insufficient amounts of prepartal treatment render the presence of the disease in the offspring most likely.

The quantitative titrated Wassermann test seems to have its greatest value in detecting nonsyphilitic infants with positive serologic reactions at birth. In the second series 74 percent of the infants presenting serologic reactions during the immediate neonatal period apparently did not have syphilis. The detection of the syphilitic infant by the use of the quantitative titrated Wassermann test alone is complicated by the facts that (a) the birth of a syphilitic infant in whom the serum reagin titer is significantly greater than that of the mother is apparently an infrequent occurrence; (b) the syphilitic, as well as the nonsyphilitic, infant may occasionally exhibit initially a decreasing titer; and (c) a significant rise in the serum reagin content may not occur for from 4 to 8 weeks postnatally.

From this study the authors say that the most accurate diagnosis of infantile congenital syphilis still calls for a close coordination in the interpretation of serologic reactions of the blood and roentgenographic changes.

Reinfection in congenital syphilis.

Richard D. Hahn. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 200-214. Mar. 1941.

The literature on second infection in congenital syphilis is reviewed. Up to the present time no indisputable second infection in a congenital syphilitic patient has been reported. In the earlier case reports the diagnosis of both the congenital and acquired infections had to be inferred from clinical appearances alone.

More recent authors usually conformed to adequate criteria for the demonstration of the acquired infection, but they accepted rather ill-defined dystrophies or purely anamnestic data as sufficient evidence for the previous presence of congenital syphilis.

The presumed significance of many of the so-called dystrophies is derived from the older clinicians and includes (especially in the French literature) practically all the ills to which human flesh is heir. Presumed reinfections in which the presence of more or less vague dystrophies is the sole evidence of congenital syphilis cannot be accepted. The first infection must be proved to be congenital.

Second infection is very rare in acquired syphilitics who have reached the latent stage before the institution of treatment. It is altogether unlikely that second infection should occur in previously untreated tardive congenital syphilitics. Yet it is this type of case which has comprised the bulk of those reported in the literature.

The first early congenital syphilitic patients adequately treated by modern standards, are now reaching an age at which the incidence of acquired syphilis is high. It is with the hope of stimulating a search for more such patients that the author reports the present cases.

The author found 104 cases of probable or possible reinfection listed in the diagnosis file of the syphilis clinic of the Johns Hopkins Hospital. Among these, only three represented reinfections in possible congenitally syphilitic patients. One of these first came under observation at the age of 8 years. This case is not included in this report due to the obvious impossibility of entirely ruling out syphilis acquired early in life. The other two are reported in detail.

These two cases conformed to rigid criteria for both the congenital and the acquired infection. In the first there were 13 years of clinical and serologic negativity, including a negative cerebrospinal fluid, between the congenital and the acquired infection. In the second, although the serologic test for syphilis at

no time became entirely negative, there were at least 8 years of clinical negativity (including a negative cerebrospinal fluid) between the congenital and the acquired infection.

Causes of prematurity. II. Comparison of maternal histories of premature and full term infants. Nina A. Anderson, Estelle W. Brown and Robert A. Lyon. *Am. J. Dis. Child.*, Chicago, 61: 72-87, Jan. 1941.

A study has been made of a total of 2,373 women admitted to the obstetric wards of the Cincinnati General Hospital who gave birth to single liveborn white and Negro infants.

For the purpose of comparison in reports which will follow this study, results have been expressed as for (a) mothers whose infants weighed less than 5 pounds 8 ounces or (b) 5 pounds 8 ounces or over, and those whose infants weighed (c) less than 5 pounds or (d) 5 pounds or over.

As diagnosed by a positive Kahn reaction, syphilis occurred in 6.8 percent of all mothers. It occurred in 8.9 percent of (a) and in 6.6 percent of (b); also in 12.5 percent of (c) and 6.5 percent of (d). A positive Kahn reaction occurred in 11.3 percent of the Negro and in 3.9 percent of the white mothers. There was a positive reaction in 5.9 percent of white mothers in class (a), in 3.8 percent of (b); also in 9.8 percent of (c), and 3.7 percent of (d). Among the Negro mothers, the reaction was positive in 11.8 percent of (a), 11.2 percent of (b); also 15.6 percent of (c); and 11.1 percent of (d).

Apparently if syphilis is associated with premature delivery, it is in the white rather than the Negro patients and in the group producing infants of the lowest birth weights.

A clinically remarkable case of congenital syphilis. M. Lutz. *Sozialhyg. der Geschlechtskr.*, Berlin, No. 5, Oct. 1940.

The case of a 23-year-old woman is reported who was first seen because of

the complaint that menstruation had not yet occurred. Both parents had syphilitic infections. The patient had had "corneal inflammation" at the age of 1 year. When she was 18 years old a chancre ulcer appeared in the region of the left elbow; shortly afterwards similar lesions appeared on the legs and about 1 year ago the face became involved as well.

Examination revealed an emaciated girl of normal intelligence in whom secondary sex characteristics were completely absent. Ulcerating lesions with purulent discharge were present on the forehead, nose, left side of the face, region of the left elbow, and both legs. The left arm was deformed and the elbow joint ankylosed. The legs were edematous. Roentgen-ray examination of the skull showed defects in the frontal bone. Only portions of the radius of the left arm remained and the ulna showed deformity. The eyes showed the typical chorioretinitis pigmentosa of congenital syphilis as well as scarring from interstitial keratitis. The blood Wassermann reaction was strongly positive. In the urine granular casts and occasional erythrocytes were found. Kidney function tests showed severe, toxic kidney damage. Neither the patient or other members of her family had received any antisyphilitic treatment.

Metastatic carcinoma of the iris, clinically simulating gumma. H. B. Stalard. *Brit. J. Ophth.*, London, 24: 541-547, Nov. 1940.

A case is described which is an example of the uncertainty of diagnosis even when based upon apparently very substantial clinical facts and signs. The patient, a male 57 years old, attended the Moorfields Eye Hospital complaining of inflammation of the left eye for 3 weeks. There was a buff-colored nodule in the iris and ciliary body. In view of the facts that the pupil of the right eye was inactive to light but reacted to accommodation, a history of syphilis 20 years before, and a present positive Wassermann reaction, a diagnosis of

gumma and syphilitic iritis of the left eye was made. In the weeks subsequent to the onset of the ocular lesion there appeared evidence of a neoplasm in the right lung and ultimately secondary deposits in the brain and viscera. The ocular diagnosis was revised to metastatic carcinoma with inflammatory features, and this was confirmed by the pathologic examination after death, which occurred 3 months later.

The author says that, as pathologist at the Moorfields Eye Hospital, he has seen 2 patients out of the hospital attendance of 276,000 in whom a secondary metastatic deposit occurred in the uveal tract. Lagleyze stated that in his experience metastatic carcinoma of the uveal tract had occurred in 1 of 100,000 patients.

Routine Kahn blood reactions. Report of 10,000 tests made on naval recruits. G. E. Thomas and R. W. Garrity. U. S. Nav. M. Bull., Washington, 39: 72-74, Jan. 1941.

This report is based on 10,000 routine Kahn tests on recruits entering the Naval Training Station, San Diego, between July 1939 and July 1940. Among these tests there were 12 persistently positive blood Kahn tests, an incidence of 0.12 percent. Ten of these men have been discharged from the naval service, and two are awaiting disposition. There were 26 strongly positive Kahn reactions which were characterized as false positives by subsequent negative findings; all returned to negative within 3 to 4 weeks after the original positive. There were also 16 weakly positive or doubtful Kahn reactions which became negative within a day or so after the weak positive. Since these were not regarded as false positives, the incidence of false positives was 0.26 percent.

After studying the series of 26 false positives in relation to cowpox vaccination, it is felt that primary and accelerated cowpox reactions may have some effect on the Kahn test. Among the 26 false positive cases, there were 11 pri-

mary reactions, 12 accelerated reactions and only 3 immune reactions, which give an incidence of 88 percent for the 23 false positive cases showing primary or accelerated reactions. There apparently is no relationship between antityphoid inoculation and the positive reactions of the Kahn test. There were no serious reactions in the group which had false-positive Kahn reactions and only 2 or 3 mild reactions. Since July 1940, blood for Kahn tests has been drawn prior to cowpox vaccination and typhoid inoculation.

Of the 12 men who had persistently positive Kahn reactions, 4 were believed to have acquired syphilis and 2, congenital syphilis; 4 had histories and physical findings that were suggestive of acquired syphilis, and 2 were definitely doubtful.

Annular papular syphilid of the tongue.

Frank C. Combes and Samuel M. Bluefarb. Arch. Dermat. & Syph., Chicago, 43: 383, Feb. 1941.

The annular papular syphilid is not an uncommon secondary manifestation in the Negro. The lesions show preference for the face, and it is unusual to find them on the buccal mucosa. The authors are reporting the first case in which they have observed the lesions on the tongue.

A Negro woman, 22 years of age, was admitted to Bellevue Hospital complaining of sores about the genitalia and anus of 2 weeks' duration. There had been a sore throat 2 weeks prior to the eruption on the genitalia. Examination showed moist papules in the anogenital region and a maculopapular rash on the trunk and extremities. An annular papular eruption was noted on the chin, on the hard palate and on the center of the dorsum of the tongue. *Spirochaeta pallida* was demonstrated by dark-field examination of material from lesions around the vulva. The Wassermann reaction of the blood was positive; the Frei test and the Ito-Reenstierna test gave negative results. All lesions responded rapidly to anti-syphilitic therapy.

TREATMENT

Ten-year survey of antiluetic therapy at the Eye, Ear, Nose and Throat Hospital. W. E. Kittredge. New Orleans M. & S. J., 93: 471-472, Mar. 1941.

Kittredge reports the results obtained in the treatment of syphilis at the Eye, Ear, Nose and Throat Hospital of New Orleans since the opening of the anti-syphilitic clinic 10 years ago. During this time 272 persons have applied for treatment, 48 percent of whom have appeared in the last 2 years. It is interesting to note that 64 patients, 23 percent of the total, had no complaint and were diagnosed by routine Wassermann tests.

There were 16 different types of lesions of the eye diagnosed as syphilitic, 11 of the nose, 7 of the throat, and 2 of the ear. The 5 most common were: 18 cases of optic atrophy, 37 of keratitis, 23 of pharyngitis, 16 of cataract, and 14 of iritis.

Nearly 40 percent of the total number of patients (105) received less than 8 weeks of treatment; only 14 patients (5 percent) received sufficient treatment to be classed as cured. Good results were obtained generally in cases of keratitis, iritis, iridocyclitis, corneal ulcers, uveitis, conjunctivitis, pharyngitis, ethmoiditis, and facial paralysis. Results were poor in cases of glaucoma, optic atrophy, macular degeneration, gumma of the septum, and sinusitis. The number of adverse reactions to treatment was negligible.

Cardiovascular and systemic morbidity following hyperpyrexia in central nervous system syphilis. Alan A. Lieberman and Charles J. Katz. Illinois M. J., Chicago, 79: 132-138, Feb. 1941.

General systemic and cardiovascular changes were studied in 173 patients with central nervous system syphilis treated at the Elgin State Hospital. Of the 173, 115 of whom were psychotic, 65 were

treated with malaria (tertian strain transmitted from patient to patient), with typhoid vaccine, 39 with both malaria and typhoid vaccine, and 19 with modified technic of typhoid vaccine therapy.

Chemotherapy was administered in all cases concurrently with fever therapy and consisted of heavy metals and tryarsamide unless contraindicated. Typhoid vaccine therapy was administered according to the Nelson divided dose technic.

The patients were kept in bed and adequate fluid intake was maintained. Nutritional standards were adhered to, including high caloric, high vitamin diet plus high caloric interval feedings. Fesol, Bland's pills, general tonics, and insulin (5 to 10 unit doses $\frac{1}{2}$ hour before meals) were given if necessary to improve the appetite.

Four patients died during or immediately following malarial treatment, two of them during convulsions, one from severe intestinal hemorrhage, and one from a facial cellulitis. Six patients given such therapy died 5 weeks to 6 months after treatment was discontinued. Inanition, bronchopneumonia, and comatose state were the causes listed. Malaria patients were susceptible to upper respiratory, urinary, and skin infections, and in three cases intestinal hemorrhage occurred.

Three patients given typhoid vaccine therapy died during the course of treatment, two from bronchopneumonia and one from acute bacillary dysentery. Another patient had temporary hematuria.

Malaria fever produced a profound generalized effect on the patients, manifested by increased morbidity and mortality, severe anemia, marked depression of the granulocytic response to infections, and a markedly prolonged convalescence. Most severe and prolonged were the changes in the cardiovascular system, in the form of hypotension and persisting electrocardiographic disturbances. The electrocardiographic changes included decrease in the amplitudes, de-

white T-wave changes, axis shifting, S-T deviations, and slurring and notching.

Typhoid vaccine produced changes which were less marked and prolonged. Hypotension and electrocardiographic changes were usually only temporary and quickly returned to normal. The mortality among patients given this treatment was limited to patients with aortitis.

The authors urge that the following criteria be applied in selecting patients for malaria therapy:

1. The cardiovascular apparatus should not show evidence of damage either clinically or fluoroscopically. Patients with aortitis should never be treated with malaria because irreversible damage occurs.

2. Patients should be in good general systemic condition.

3. If the blood pressure decreases between paroxysms to less than 70 per cent of its original systolic basal level, the situation is considered desperate and the malaria treatment should be discontinued. Electrocardiograms must be taken before the institution of treatment and after the fourth chill, in order to evaluate myocardial insufficiency and prevent frank or impending collapse. Adequate support must be given to the hematopoietic system; iron compounds, reticulin, high caloric feedings, and vitamins are essential.

The criteria in typhoid vaccine therapy do not have to be as rigid.

In those cases treated with combined malaria and typhoid vaccine, although the vaccine fever itself did not seem to aggravate the changes resulting from malaria, it was deemed expedient to wait for 2 to 3 months following interruption of malaria therapy before further fever was administered.

Kirschbaum, in the discussion, stated that three causes of death from malaria therapy are as follows: (1) The brain infection by the malaria plasmodia which occlude the smaller brain arteries and capillaries producing thrombi and hemorrhage. (2) Myocarditis and heart failure. (3) The general septic stage

involving all the bodily organs. These causes of death may be combined.

Factors influencing the course of syphilis. Hugh J. Morgan. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 233-250, Mar. 1941.

The author describes the so-called "typical course" or general pattern of syphilis in man. He stresses the fact that the disease does not always conform to this pattern. The human body is noted for the vagaries it exhibits when reacting to infection with *Treponema pallidum*.

He considers a few of the factors responsible for the protean nature of the disease. Some of these factors are indigenous to the host; others, to the parasite; and still others, to the environment in which the host and parasite exist.

The factors discussed which influence the course of syphilis are as follows:

1. Race: No true racial immunity exists. Turner found Negroes to be more susceptible than white persons to certain types of skin lesions, bone involvement, iritis, and aortitis. Cardiovascular syphilis was found to occur about twice as frequently in Negro as in white males. Tabes and paresis occurred much less frequently in Negro than in white patients. In experimental syphilis anthropoid apes have been found much more susceptible to syphilis than lower animals.

2. Age: Syphilis developing during intrauterine life is commonly fatal. Infants and very old patients seem to have the disease more severely than do members of other age groups. In experimental syphilis, Chesney noted that younger animals had more violent initial lesions than older ones, although subsequent generalized lesions were somewhat slower in developing and were less severe in character and extent.

3. Sex: Syphilis in the female produces much less conspicuous manifestations than syphilis in the male. In the clinics men with acute syphilis greatly outnumber women with such manifestations. Women outnumber men among

patients with latent and chronic syphilis. The incidence of cardiovascular syphilis and central nervous system syphilis is lower in women than in men. Moore has emphasized the beneficial influence of pregnancy upon the course of syphilis in women and has called attention to the fact that cerebrospinal fluid abnormalities were twice as frequent in a group of sterile women as in a comparable group of women who had become pregnant at the time of or following infection.

4. Environment: Intercurrent infections may modify the course of syphilis. Neurosyphilis commonly progresses unfavorably in the presence of acute respiratory infections. Syphilis or antisyphilitic infection may unfavorably influence the course of tuberculous infection. Hypertension predisposes to the development of aortic regurgitation in persons with syphilitic aortitis. Trauma may influence chancre formation, and it may result in the localization of the widespread skin and mucous membrane lesions of early syphilis. Gummatous lesions occasionally develop in surgical scars, in traumatized testes, and in fractures.

5. Specific treatment: The specific treatment of early syphilis is designed to cure the disease, or to arrest it and prevent serious late sequelae. Sometimes, however, specific treatment not only fails to accomplish these ends but exerts an unfavorable influence upon the course of infection. The commonest factor predisposing to the development of acute syphilitic meningitis or cranial nerve inflammation is some, but inadequate, specific treatment. The author discusses the reason for this phenomenon.

6. Nonspecific treatment: Trypan blue and lecithin in experimental syphilis in animals and fever therapy in clinical syphilis are discussed. The beneficial effect of trypan blue and lecithin in rabbits seemed to be brought about by a speeding up of the reparative processes of the body by the plasmatocytes rather than by any direct action of the latter on *T. pallidum*. This may throw light on

the mechanisms involved in other forms of nonspecific therapy, including malarial inoculation. In acute syphilis elevation of the body temperature inhibits the natural progression of the disease, and leads to the destruction of *T. pallidum*. This inhibition by fever probably cannot be utilized alone to any great practical advantage in the treatment of early syphilis. It has been employed as an adjunct to chemotherapy. The thermal factor may contribute to the striking seasonal variation which characterizes the disease manifestations of rabbit syphilis. It is very difficult to induce typical active syphilis in rabbits during very hot summer months unless the rabbits are kept in a cool place. Sunlight and diet may also effect significantly the course of the experimental disease.

7. *Treponema pallidum*: It has not yet been proved that there are strains of the organism which, when present in man, exhibit predilections for certain tissues or organs. Experiments have been performed which indicate that the quantity of the virus is important in determining the course of syphilitic infection, although differences in the quality of the virus have not been proved to be significant factors. In experimental syphilis it has been found that the larger the dose of organisms injected into the rabbit, the shorter the incubation period of the disease. Single organisms injected intratesticularly in the rabbit have not induced infection. In human condyloma counts of organisms have ranged from 3,700 to 246,000 *Treponemata pallida* per cubic millimeter. Counts on fluid from eight chancres varied from 370 to 29,500 per cubic millimeter. If the susceptibility of some human beings to infection with syphilis is as great as that of some rabbits studied (and there is good reason to believe that it is), an inoculum of less than 1/150 cubic millimeter of human chancre fluid or less than 1/375 cubic millimeter of condyloma fluid may result in infection with syphilis.

changes in the electrocardiogram and in the cardiac rhythm during the therapeutic use of potassium salts. Harold J. Stewart and J. James Smith. *Am. J. M. Sc., Philadelphia*, 201: 177-197, Feb. 1941.

This is a report of certain effects of the therapeutic use of potassium salts in 5 cases. Three of the patients had cardiovascular syphilis (1 had syphilitic aneurysm of the aorta, 1 had syphilitic heart disease and aortic insufficiency, and a third had syphilitic heart disease with aortitis and aortic insufficiency).

Two of three patients with syphilitic heart disease showed electrocardiographic changes in the form of the T waves and ST segments while taking potassium iodide. These changes disappeared when the drug was discontinued. The changes in T waves in the electrocardiograms of these patients were attributed to coronary occlusion before their association with the use of potassium iodide was uncovered. When potassium iodide was discontinued, the electrocardiograms reverted in form. Since patients with syphilitic heart disease frequently show changes in the electrocardiogram similar to those seen in coronary occlusion, it appears from the evidence presented here that some of the cases require reevaluation. The electrocardiographic effects may be induced by the administration of potassium iodide near the time of recording the electrocardiogram.

The following toxic manifestations were seen in the five patients: Sinus tachycardia, supraventricular paroxysmal tachycardia, complete auriculoventricular dissociation with irregularity of the ventricles suggesting ventricular fibrillation, progressive first-degree heart block, and auricular standstill. These toxic effects, with the exception of auricular standstill, disappeared with discontinuance of potassium iodide.

Because of the widespread use of potassium iodide in the treatment of cardiovascular syphilis and of hypertension, the authors emphasize that its use is not without danger. They urge that the administration of the drug be

carefully supervised if toxic effects on the heart are to be recognized and their occurrence prevented.

Hemorrhagic encephalopathy due to acetarsone. Harry L. Segal. *Ann. Int. Med., Lancaster*, 14: 1083-1088, Dec. 1940.

Segal reports the case of a woman, aged 64, who had received 4.5 gm. of acetarsone in 9 days in treatment for bacillary dysentery (0.25 gm. twice daily). On the ninth day fever, nausea, and macular eruption occurred, followed 2 days later by coma, convulsions, and opisthotonus. It was feared she might die in any one of the spells. The administration of sodium luminal lessened her convulsions and that of adrenalin seemed definitely life-saving. The spinal fluid showed 1,750 to 5,000 red blood cells per cubic millimeter and 56 white blood cells per cubic millimeter. Following this, recovery took place with the exception of marked pain and paresis in the arms and right leg, with pains and weakness still persisting in left upper extremity 1½ years after the ingestion of the acetarsone.

The literature is reviewed. Opitz, in 1930, reported severe cerebral illness following the use of acetarsone, and Aschner added a case. In 1932, Reiter included these cases in his review of the German literature, as well as 3 cases which had appeared in the French literature and a case of his own. Since Reiter's article no further case of definite encephalopathy following acetarsone has been reported until the present case.

The author warns against the indiscriminate use of acetarsone, especially when other more efficacious and less dangerous drugs are available.

Excretion of sulfanilamide in breast milk. Questions and answers. *Arch. Ophth., Chicago*, 25: 359-360, Feb. 1941.

In this letter, the inquiring physician states that he was called to treat a baby 4 days old for gonorrheal conjunctivitis. The baby's mother at this time was taking large doses of sulfanilamide. The ques-

tion arose as to whether or not the sulfanilamide taken by the mother would be transmitted through the breast milk to the baby. The infant was given an initial dose of 0.32 gm. of sulfanilamide in water per kg. of body weight. The second day the dose was increased to 0.65 gm. per kg. per day. After the third dose the baby's skin had a blue tinge which lasted 2 hours. The next day the first dosage was given, and the child did not have any untoward effects. Sodium bicarbonate was administered with the sulfanilamide. There was no rash. The inflammation and swelling of the lids (caused by the conjunctivitis) disappeared by the fourth day. The secretion was still fairly free, with no trace of blood. There was no evidence of injury to the corneas.

The inquirer states that he has treated many small children ($1\frac{1}{2}$ to 4 years of age) with sulfanilamide for gonorrheal conjunctivitis, but this is the first baby he ever treated whose mother was taking sulfanilamide at the same time. He asks what quantity of sulfanilamide is carried by the mother's breast milk to the baby, and what allowance in dosage for the baby should be made.

The answer stated that sulfanilamide is excreted in human breast milk in concentrations which vary but which usually approximate 80 percent of the concentration of the drug in the blood. With average doses of sulfanilamide which might be given to the lactating mother it would be unusual for the baby to obtain from the breast milk as much as 1 grain (0.06 gm.) of the drug in 24 hours. Therefore, this factor would play no appreciable role, as a rule, when nursing infants are treated with sulfanilamide.

Five references on the subject are listed.

The treated cases of gonorrhea in the university clinic for skin diseases, Leipzig, 1930-1939. An example to prevent false conclusions from the statistics. *Sozialhyg. der Geschlechtskr.*, Berlin, No. 3, June 1940.

During the decade 1930-1939 an average per year of 288 women were treated for

gonorrhea in the clinic. In 1939 the average was 311, showing that there was definite tendency either to an increase or a decrease in the number. The average number per year for the men during the decade was 277, whereas for the year 1939 the average was 246. The average number of days per year of treatment was 13,682 for women and 11,203 for men. Since the values for 1939 were only 8 percent for the women and 7,499 for the men, one might conclude from this that a considerable decrease in the number of cases had occurred, but such conclusion would only be justified if one could establish a period of treatment for each individual case which would remain approximately the same. As a matter of fact, the average duration of treatment has been considerably decreased since 1938 when chemotherapy was introduced. If the average duration of treatment per year for the years 1930-1937 is compared with that of 1939, it is found that there was a decrease from 51 to 28 days for women and from 42 to 30.5 days for men. In other words, the average duration of treatment has been decreased by 45 percent in women and by 29 percent in men. With such marked change in the average duration of treatment as has been observed in gonorrhea since 1938, a decrease in the total number of treatment days occupied beds does not give a clue to the frequency of the disease itself.

Cutaneous and conjunctival manifestations of sulfathiazole intoxication

Italo F. Volini, Robert O. Levitt, and Hugh B. O'Neil. *J. A. M. A.*, Chicago, 116: 938-940, Mar. 8, 1941.

If the nausea and vomiting induced by sulfapyridine are not considered, cutaneous rashes are probably the most frequent toxic reaction encountered from the new chemotherapeutic drugs. Cutaneous eruptions and conjunctivitis are frequently seen on medication with sulfathiazole. The rashes encountered are urticarial, erythematous, macular, papular, nodular, and purpuric. Of these, the nodular is definitively different from any nodular lesion seen before, and it prob-

presents the advanced stage of toxic rash developing on continued medication. In the authors' experience it has been the most serious lesion, having been associated with a fatal outcome in a high percentage of cases.

In a series of 180 patients treated with sulfathiazole, there were 7 in whom a rash developed during treatment, or an incidence of 3.9 percent. The average dose of sulfathiazole in this series was 26 gm. The average dose given the 7 patients in whom rashes developed was 34 gm. There were 3 deaths among these 7 patients, the cause of death being severe pneumonic disease. These 3 patients had been given 51, and 75 gm. respectively. One patient with a maculopapular rash who survived received a total dose of 59 gm. In 4 patients the manifestations appeared after 5 days of use of the drug. The average blood sulfathiazole concentration in the patients with eruptions was 4.2 mg. per 100 cc., which is about that found in the entire series. There seems to be, therefore, no definite correlation between the level of the drug in the blood and the development of the rash. The total dosage shows a closer relationship. Sensitization may follow resumption of interrupted medication.

Involvement of the conjunctiva was noted in 4 of the 7 cases of rash; only 1 case of severe conjunctivitis was seen which was unassociated with cutaneous eruption. The conjunctivitis rapidly cleared, and no permanent changes were noted.

Cessation of administration of the drug is immediately indicated upon appearance of the rash; this may prevent further toxic developments.

Sulfathiazole therapy of gonorrhea. J. H. Greig, J. L. Uren and D. R. Mitchell. *Canad. M. A. J.*, Toronto, 4: 237-239, Mar. 1941.

The results of treatment of 120 cases of gonorrheal urethritis in the male with sulfathiazole are presented from the Toronto General Hospital. These patients were unselected, and their average age was 25 years. In 85 percent the urethral

discharge was confined to 7 days or less. The rate of cure among the 96 cases who had had no previous form of therapy was 92.7 percent; among the 24 cases who had failed to respond to one or more courses of sulfanilamide or sulfapyridine, it was 90.6 percent. The criteria of cure required that there be a complete absence of clinical evidence of the disease, that repeated smear and culture examinations be negative, and that the two-glass test of urine be free of pus and shreds. Patients were observed for a period of 6 weeks following cessation of chemotherapy.

The routine dosage was 1 gram 3 times a day after meals for 5 days, with 1 gram on retiring also on the second and third days. The majority of patients received 17 grams and were cured in 3 days. It was not considered advisable to administer the drug beyond the 5-day period.

Nine cases were failures. In 3 cases there was evidence of reinfection and in 3 other cases the discharge recurred after an asymptomatic period of 4 to 10 days after the drug was discontinued. Ten patients had mild toxic reactions which did not interfere with their normal activities.

Silver nitrate ampules. Samuel R. Damon. *J. M. A. Alabama, Montgomery*, 10: 281, Feb. 1941.

For years, silver nitrate solution has been distributed by the Bureau of Laboratories of the Alabama Department of Public Health to physicians, midwives, and nurses in the State. This solution was dispensed in white or yellowish-white wax ampules which were accompanied by instructions to the effect that the solution should not be relied upon for the prevention of ophthalmia neonatorum if the wax was at all discolored. It was thought that discoloration indicated some degree of precipitation of the silver nitrate due to decomposition. This precipitation occurred on exposure of the ampules to light for a considerable length of time.

To make sure that light does not reach the drug, a small amount of inert coloring matter, lamp-black, is now added to the

beeswax in the manufacture of the ampules. Thus, light is excluded from the silver nitrate.

The new ampules, therefore, are black even when freshly prepared. Attention should be focused on the expiration date of each package rather than on the color of the ampules, in determining whether the drug is fresh enough to use.

Etiologic considerations in postarsphenamine dermatitis. Frank E. Cormia. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 189-199, Mar. 1941.

Postarsphenamine dermatitis develops in from 0.3 to 1 percent of all patients treated with trivalent arsenical drugs. It causes from 5 to 20 percent of the fatalities from arsenical therapy. This is as many as, or more than, result from severe liver damage. In this respect it is exceeded only by deaths following hemorrhagic encephalitis. Because of it, arsphenamine therapy must be permanently discontinued in many patients.

Dermatitis from the arsphenamines in human beings is largely a manifestation of epidermal sensitiveness of the delayed cellular type. It is caused by previous exposure and is made manifest by subsequent exposure to the same or to related arsphenamines. The initial exposure is probably intradermal in most instances, since the arsphenamines are indifferent antigens in humans and since there is general acceptance that the intradermal route offers the highest degree of resulting sensitization in varied forms of experimentally produced allergy. The mechanism of spread is unknown, but it may occur through the lymphatics of the skin to the blood stream and thence to distant cutaneous areas. Sensitization develops after a variable period of time and may usually be demonstrated by the patch test.

Possible variations in the chemical structure of the drugs and superimposed local tissue injury increased the ease and degree of sensitization in some cases. The skin is further predisposed to react when a previous contact type of dermatitis has occurred. Conversely,

other sensitivities may develop as a result of arsphenamine sensitiveness.

It has been found that diets deficient in vitamin C greatly increased the with which sensitization to neoarsphenamine was produced in animals. Patients with previously involuted postarsphenamine dermatitis, confirmed positive patch tests, were given 500 mg. of vitamin C intravenously daily for 5 days. After this the same brand of arsenical which had caused the previous dermatitis was administered to them cautiously, with minute initial doses. All of the six patients had positive patch tests at the onset of the experiment. Vitamin C levels were kept high throughout by the subsequent oral administration of 100 to 200 mg. daily. Five of six patients eventually took full doses of the arsphenamine without further cutaneous reaction, and the patch test came negative in three of four patients subsequently tested.

The author has not been able to determine the rationale of the inhibiting effect of vitamin C therapy in patients with previous postarsphenamine dermatitis. The effect is not always a complete one. In several patients vitamin C has prevented the return of the dermatitis following even minute doses of arsenic.

A definite relationship between liver damage and postarsphenamine dermatitis has not yet been demonstrated. Liver damage may reduce the plasma and tissue vitamin C level from fasting intestinal absorption. Initial low vitamin levels, with reduced glycogen formation, may predispose to liver injury from arsenic.

Injury to the reticulo-endothelial system may occur, but it would seem to be incidental to liver or bone marrow injury. Capillary damage cannot be excluded as a factor in the production of dermatitis and may be present in the frequent transformation of vascular toxic erythema into actual dermatitis on continuation of arsphenamine therapy. A causal relation between such damage and arsphenamine dermatitis is, as yet, hypothetical.

is not proved by experimental work. Experimental proof of any linkage between cutaneous sensitivity and change in the sympathetic nervous system is likewise lacking.

Four cases are presented which illustrate some of the phases of the etiologic mechanisms of postarsphenamine dermatitis.

Surgery in syphilitics. With a study of cases in mental hospitals: 104 cases reported. George A. Wiltrakis, Anthony V. Partipilo and Louis Olsman. Illinois M. J., Chicago, 79: 141-144, Feb. 1941.

A survey was made of 997 operations performed during the past 2 years at Elgin and Chicago State Hospitals. The surgical results in 104 patients with syphilis (26 with systemic and 78 with neurosyphilis) were compared with the results in 818 nonsyphilitic patients.

There were no deaths among the patients with systemic syphilis. The mortality rate among the 997 patients was 1 percent; among the 818 nonsyphilitic patients, 3.66 percent; and among neurosyphilitic patients, 6.41 percent. Among a group of 75 on whom no serologic tests for syphilis were made (chiefly employees of the hospitals) there were 3 deaths. A total of 922 operations were performed on mental patients.

There were 391 major operations performed—324 on nonsyphilitic patients, 26 on neurosyphilitics, 13 on patients with systemic syphilis, and 28 on patients who have not tested. There were 30 deaths among these nonsyphilitics (9.25 percent of the 324), 5 deaths among the neurosyphilitics (19.23 percent of the 26), no deaths among patients with systemic syphilis, and 2 deaths among 28 employees who had major operations.

There were 606 minor operations, with only 1 death (an employee).

The authors believe that syphilis was a definite contributing factor in the death of only two patients. One of these had a hydrocelectomy, with death resulting from bronchopneumonia. The other pa-

tient (a poor surgical risk) died of cardiac failure and bronchopneumonia following an emergency enucleation of an eye for panophthalmitis. Syphilis was a factor contributing toward the poor physical health of these patients. Two other neurosyphilitic patients died of peritonitis following operations for perforated appendices with abscesses, and a third died following an operation for miliary tuberculous abscesses and peritonitis. In these three cases the prognosis would be poor in any patient, and syphilis probably contributed little if anything toward their deaths. Thirty rectal and 28 gynecologic operations were performed with no deaths.

The mortality of the neurosyphilitic patients was higher, according to the statistical study. However, after analyzing the causes of death the surgical risk of the neurosyphilitics seemed comparable to that of nonsyphilitics.

Local surgical complications were more numerous in the neurosyphilitics, but these were chiefly wound infections. Difficulties in wound healing (sloughing, evisceration, and gumma formation) did not occur. Excluding the infections, the wounds of syphilitics healed as well as those of nonsyphilitics.

The authors state that if syphilitic patients have had adequate antisymphilitic therapy in the past, they can safely have emergency and elective surgical operations without additional specific treatment or delay.

PATHOLOGY

A study of syphilis of the aorta and aortic valve area. Charles F. Nichols. Ann. Int. Med., Lancaster, 14: 960-977, Dec. 1940.

An analysis of 41 cases of syphilitic aortic incompetency, which came to autopsy but were not studied clinically, was made in connection with the diagnosis of uncomplicated syphilitic aortitis. The

average age of this group was 42.1 years. There were 30 Negroes and 11 white patients, and 27 male and 14 female. The average duration of symptoms before hospitalization was 6.2 months. In 26 cases the chief presenting symptom was dyspnea on exertion, later followed by cough and ankle edema. In all the 8 cases which presented paroxysmal pain there was valvular deformity, but in 3 the left and in 4 the right coronary ostium was completely closed while in 1 both ostia were barely visible. Anoxemia of the heart muscle must have been a marked factor in the production of pain. The duration of symptoms in these 8 cases was no longer than for the group which showed no coronary involvement. The entire group was diagnosed while under observation as aortic incompetency and myocardial failure of the congestive type. The Wassermann reaction, taken in 35 of these cases, was positive in 34 and negative in 1. A syphilitic involvement of the aortic valve area was found in all and varied from widening of the commissures to thickening and fibrosis of the valve leaflets with shortening and retraction.

Seventy cases of active syphilitic aortic insufficiency admitted to medical service of the Philadelphia General Hospital were studied. There were 53 Negro and 17 white patients; 60 were male and 10 female. The average age was 46.04 years. From information given in 34 cases, there was a long latent period, varying from 5 to 40 years, between the initial infection and the onset of symptoms. The most frequent early symptom was dyspnea on exertion, and this was present in 71 percent of the cases. In only 6 cases was paroxysmal dyspnea a factor in the onset. There were no cases which could be classified as having pain of the angina pectoris type. In 12 patients pain was a moderate factor in the mitral symptoms and was usually substernal. In 20 patients, tightness or oppression under the sternum was emphasized. The average duration of symptoms before the patient

was forced to seek hospital attention was 10 months. In 40 percent, edema of the ankles was present upon admission to the hospital. An increase in the size of the heart was noted in 93 percent, and the typical to-and-fro murmur of aortic insufficiency was present in 87 percent. In 5 cases a peculiar musical diastolic murmur was heard. The average pulse pressure in this series was 84 mm. of mercury, which emphasizes the clinical fact that a collapsed pulse is frequently associated with high pulse pressure. The Wassermann reaction was positive in 60 (85 percent) of these cases, negative in 6, and not noted in 4.

The fluoroscope alone should not be used for diagnosis. Only when the fluoroscopic findings are suggestive can they be correlated with a corroborative history, serologic and physical findings should the diagnosis be made. The electrocardiograms for this series showed an absence of noteworthy features. Rheumatic heart disease probably causes the greatest difficulty in differential diagnosis, but the rheumatic heart practically always comes to the observation of the clinician before the age of 30, while syphilis of the aorta usually manifests itself between the ages of 35 to 55. The similarity with which the type of heart failure in syphilitic aortic insufficiency progresses is striking and is totally different from the type of failure observed in the hypertensive, rheumatic, and coronary artery groups. After the appearance of symptoms the condition is slightly amenable to treatment and the progress is rapidly downward.

The pathogenesis of gonococcal infections. Wesley W. Spink. *Bull. Ch. Infect. Dis.*, Boston, 4: 1-2, 1941.

It is a curious phenomenon in nature that gonorrhea cannot be experimentally produced in the lower animals; the gonococcus seems to be exclusively a parasite of human tissue. The gonococci quickly penetrate beneath the surface of the mucous membrane. In the anterior ure-

the male, gonococci have been found between the intercellular spaces well below the surface epithelium within 36 hours after exposure. This would imply that before the onset of clinical signs and symptoms of gonorrhea, the coccus is well beyond the reach of germicides applied to the surface.

While specific data are lacking it is quite probable that gonococci invade the blood stream more often than is appreciated. The more common metastatic lesions which may result from gonococemia include arthritis, tenosynovitis, conjunctivitis, iritis, and iridocyclitis. Because of the serious consequences resulting from the invasion of the blood stream by the gonococcus, specific therapy with the sulfonamide compounds should be instituted as soon as the diagnosis of gonorrhea is made. Spink does not subscribe to the policy of waiting until the patient may have built up his immunity before beginning chemotherapy.

It is believed that sufficient clinical data are now available to predicate the thesis that the coccus will remain passively in the body and give rise to an acute infection years after gonorrhea has been acquired. However, such a sequence is relatively uncommon.

Occasionally conjunctivitis and iritis accompany gonococcal arthritis, and gonococci are invariably absent in the exudate of the eye. Likewise, skin lesions such as keratoderma blennorrhagicum fail to yield the organisms when appropriate culture techniques are applied. Further inquiry is necessary before the true status of these lesions is known. Precise knowledge is also lacking as to whether strains of gonococci vary in their virulence and invasiveness. It is known that under experimental conditions the gonococcus may be rendered "dig fast" to both sulfanilamide and sulapyridine. The widespread and indiscriminate use of these drugs may possibly be followed by the propagation of gonorrhea refractory to therapy with these compounds, because of the development of resistant strains.

LABORATORY RESEARCH

The blood cells in early syphilis. Udo J. Wile, Raphael Isaacs and Charles W. Knerler. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 133-141, Mar. 1941.

At the present time no specific quantitative variations in the blood have been reported which can be used to supplement a biologic test in diagnosing a questionable case of early syphilis. If abnormal cells which occur only in syphilis could be demonstrated, the blood picture would be important. To investigate this feature, the blood cells of a series of 36 patients with early syphilis and those of 9 rabbits with early experimental syphilis were studied. Emphasis was placed on the type of cells found in the peripheral blood.

Mild anemia of the secondary type, monocytosis, and eosinophilia were noted. These variations had been reported previously by other investigators.

In none of the previously published articles was any mention made of plasma cells specifically. In this study, however, plasma cells were found in the blood of 29 (80 percent) of the 36 untreated patients with early syphilis and in 39 (88 percent) of 45 specimens of blood from these patients after they had been given some treatment. This finding was confirmed in the blood of experimental animals, in which plasma cells were found in 8 of 9 cases (about 90 percent). Isaacs (one of the authors) thinks that this is a nonspecific reaction which occurs whenever lymph nodes are involved in the disease process. In view of the regularity of involvement of the lymphatic system in syphilis, plasma cells may be expected consistently in syphilitic blood pictures (just as they were found in these cases).

Still another cell which is foreign to the normal blood picture and which has not been reported previously was noted quite commonly in these cases. It was a cell similar to the type seen in infectious mononucleosis. It was noted in two stages, young (early) and old (late), and it had the following characteristics: (1) In its younger state in films stained with Wright's stain, it measured (on the average) 12.0 by 13.5 microns, with a nucleus 12.0 by 7.5 microns. The cytoplasm was deeply basophilic, nongranular, but with a "curdled" texture. There was no perinuclear clear zone. The material in the nucleus was finely divided with a flaky texture. There was no sharp nuclear membrane. The nucleus was usually oval or kidney-shaped. (2) In the older form the average measurements were 15.0 by 15.75 microns, with a nucleus of 9.0 by 13.5 microns. The intense blueness of the stained cytoplasm was confined to the edge, frequently with blue-staining wedges extending into the cytoplasmic area. The cells were nongranular.

With brilliant cresyl blue, followed by Wright's stain, the cresyl blue precipitate in the cytoplasm was confined to small clumps, surrounded by a clear, non-staining cytoplasm. This differed from the rather uniformly distributed cresyl blue network of the lymphocytes and the fine granules (interspersed with red-staining granules) of the monocytes.

In untreated patients with early syphilis these cells were seen in 22 of 36 cases (61 percent) and in 35 of 45 cases (79 percent) shortly after treatment was instituted. They were present in some cases in which Kahn reactions were negative. They were absent in some with positive serologic tests.

There seems to be no direct correlation between biologic tests for syphilis and the presence of these cells in the blood, although such a relationship is suggested by the frequency of positive serologic tests for syphilis in cases of infectious mononucleosis in which similar cells are seen. Infectious mononucleosis is the only other condition in which this type of cell is found.

In the blood films of 8 out of 9 syphilitic rabbits (about 90 percent), cells were found which were comparable to the abnormal cells seen in the blood of patients. Such cells were not seen in the blood of normal rabbits.

On the possible presence of a reagin-factor in normal human serum. N. Sherwood, Glenn C. Bond and R. Canuteson. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 179-185, March 1941.

By the use of a widespread Kahn test, using serum-antigen ratios varying from 100:1 to 1:5, a positively reacting substance was found to be present (perhaps temporarily) in the blood serums of 3 among 1,017 presumably healthy, nisyphilitic white American university students of both sexes. This flocculation extended to the diagnostic range of the Kahn test in only two serums.

Of 15 students who gave positive or doubtful results by one or more techniques, 2 reacted only with the Kline and Eagle tests. It is probable that these Kline and Eagle tests were nonspecific either to highly sensitive antigen or to laboratory errors. They probably do not reflect the presence of a reacting substance in the two serums tested.

Six of the 13 serums were positive only by the widespread Kahn technique, using serum-antigen ratios significantly in excess of those used in the diagnostic tests. In these 6 cases the other tests were negative.

In the remaining 7 cases the widespread Kahn test was positive, giving definite flocculation over a variable range of serum-antigen ratios, which in the case of 2 serums actually extended to the diagnostic range (the standard Kahn test also being positive). In these cases one or more of the other diagnostic tests used also gave positive or doubtful, inconclusive results.

In 9 of the 13 with originally positive widespread Kahn tests, it was possible to repeat this test on subsequent specimens obtained at varying intervals over a period of 8 months. In 5 of these

reagin-like substance was present in one or more repeat tests but eventually disappeared. In the other 4 the original positive tests could not be repeated. It is possible that this change in reactivity was due to the use of a different antigen in some cases. If so, the original positive result might be interpreted as a technical error. It is also possible, however, that the serologic reversal noted in these 9 students represented the spontaneous disappearance of "normal reagin" and that normal human serums occasionally (even if only temporarily) may contain a substance similar to that present in syphilitic serum. In rare persons this normal factor may conceivably be present in sufficient concentration to give biologic false positive or doubtful agnostic tests for syphilis.

The levulose tolerance test in intolerance to antisyphilitic therapy. Gordon O. Horne. *Edinburgh M. J.*, 47: 801-804, Dec. 1940.

Horne has employed liver function tests in patients receiving antisyphilitic treatment with arsenic and bismuth. He desired to study the cause of jaundice occurring during the course of antisyphilitic treatment, and he felt that by detecting liver damage prior to its clinical manifestation the occurrence of toxic jaundice might be anticipated and so prevented. The levulose tolerance test was employed in a series of 24 cases taken at random to determine whether it might be used in detecting liver damage prior to the development of clinical signs. In all cases, intolerance occurred during the course of treatment with an organic arsenical and a metallic bismuth preparation. Some of the cases were under treatment in the hospital, some were hospitalized for the test, and some were investigated as out-patients.

In 7 out of 20 cases where clinical jaundice was present, the levulose tolerance test was normal to both the Swart, Scarborough and Davidson, and the Tallermann standards. Six cases only were abnormal according to the first standard, and all of these and the re-

maining 7 of the 20 cases were abnormal to the second standard. One case which showed intolerance in the form of urticaria gave a normal curve to both standards, and only 1 of 6 cases showing skin manifestations gave an abnormal curve. In 4 cases the test was repeated after the jaundice had cleared up, and all were found to be normal according to both standards.

The failure of the levulose tolerance test to demonstrate liver dysfunction in such a large proportion of cases, even where clinical jaundice was present, does not seem to warrant its employment during the course of treatment in order to anticipate intolerance prior to the appearance of clinical signs.

Effect of temperature on Kahn reaction.

II. With serologically positive sera of human syphilis. R. L. Kahn, E. B. McDermott and S. Marcus. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 157-161, Mar. 1941.

When serologically positive serums of presumably syphilitic humans were examined with the Kahn test under proper conditions at 37° and at 1° C., they showed a tendency toward more marked precipitation at 37° than at 1° C. This tendency was demonstrable with moderately positive serums without the need of diluting them with salt solution. The tendency was also demonstrable with strongly positive serums after they were diluted with salt solution to a degree that they gave moderate or weak serologic reactions. In another report by these authors (*Am. J. Syph., Gonorr. & Ven. Dis.*, 25: 151-156, Mar. 1941) it was shown that serologically positive, nonsyphilitic animal serums showed a reverse tendency—marked precipitation at 1° C. and weak or no precipitation at 37° C. These findings indicate the existence of two types of seropositive reactions—a syphilitic and a nonsyphilitic type.

Among the human serums tested were a small number of lyophile serums submitted by Senior Surgeon J. F. Mahoney, Director of the Venereal Disease Labora-

tory of the U. S. Public Health Service at Staten Island. These serums also showed a tendency toward stronger precipitation at 37° than at 1° C.

Results with another group of serums sent to the authors by Mahoney's laboratory for the purpose of comparing Kahn reactions with those given by other serologic methods, further demonstrated this tendency. Of a total of 195 serums examined, 101 were Kahn positive, and 92 were negative. Of the positive serums, 100 gave more marked precipitation at 37° than at 1° C., while one serum gave precipitation results of a reverse type. Of the negative serums, 90 proved to be negative at all temperatures, while 2 showed moderate precipitation at 1° C. On the basis of examination of more than 2,000 serums at the differential temperatures, the authors state that it is probable that the 100 positive serums which gave more marked precipitation at 37° C. were of syphilitic origin, while the one serum which gave more marked precipitation at 1° C. was of nonsyphilitic origin.

It was of interest to determine whether different specimens of blood obtained at different intervals from the same syphilitic patient would give consistent precipitation results at 37° and at 1° C. The results obtained with the blood serum of three patients receiving anti-syphilitic therapy showed that this property of syphilitic serums is apparently constant.

Occasionally, moderately positive serums gave the same precipitation results at 37° and at 1° C. If diluted sufficiently with salt solution, such serums generally gave stronger precipitation at one of the two temperatures. If no differentiation was obtained at these two temperatures, the results were considered inconclusive.

Effect of temperature on Kahn reaction

III. With serologically positive serum the absence of syphilis. R. L. Kahn, E. B. McDermott and S. Marcus. *Ann. J. Syph., Gonorr. & Ven. Dis., St. Louis* 25: 162-172, Mar. 1941.

Two basic types of verification reactions have been noted with serologically positive serums: (1) A syphilitic type, when a serum showed more marked precipitation at 37° than at 1° C.; and (2) a general biologic type, when a serum showed more marked precipitation at 1° than at 37° C. Reactions which were atypical were reported as inconclusive. In a broad sense, the syphilitic and general biologic types corresponded to the presence and absence of syphilis, respectively.

In this article the authors report the results of further studies of serologically positive serums from persons with leprosy, malaria, and other nonsyphilitic pathologic conditions. Blood specimens from leprosy cases were obtained from the National Leprosarium, Carville, Louisiana. Those from malaria cases were obtained from the Milledgeville State Hospital in Georgia. Other serologically positive serums from presumably nonsyphilitic patients were obtained from different sources.

It was observed that serums from seropositive patients with leprosy were divisible into two main groups: (1) Those that gave marked precipitation at 37° C. with little or no precipitation at 1° C., and (2) those that gave marked precipitation at 1° C. with little or no precipitation at 37° C. The data relating to 20 serums are tabulated. Ten of these serums showed the syphilitic type of reaction and 10 showed the general biologic type. Of interest is the finding that most of the 10 serums which gave the syphilitic type of reaction were quite potent and required relatively high dilution with salt solution in order to bring out differential precipitation at 37° and

C. Most of the 10 serums which gave the general biologic type of reaction were of low potency and required little or no dilution with salt solution to bring out differential precipitation. This indicates that the syphilitic type of reaction in leprosy is generally accompanied by high serologic titers and the general biologic type of reaction by low serologic titers. At present, there is no clinical criterion by which it can be determined with certainty that the leprosy cases giving the syphilitic type of reaction have syphilis and those which give the general biologic type of reaction are free from this disease. Of 44 serologically positive serums from persons with leprosy, 11 gave the syphilitic type of reaction, 12 gave the general biologic type. Serologic tests were made on a group of nonsyphilitic persons with malaria. In each case the Kahn reactions were repeatedly negative before the patients were given malaria. They became positive for a limited period after the malaria developed and then became negative again after recovery. Verification tests of serums taken from these patients during the Kahn-positive period persistently gave the general biologic type of reaction.

In the miscellaneous cases of patients diagnosed as nonsyphilitic, the seropositive results with a diagnostic test were accompanied by the general biologic type of reaction with the verification test. The clinical conditions included inflammatory pelvis, arteriosclerosis, multiple sclerosis, obesity, bronchiectasis, and diabetes. One of the persons listed was a blood donor who was apparently normal. Thus, the verification test is capable of detecting nonspecific types of reactions occurring in the presence of various pathologic conditions. Of special interest is one case in which the patient showed a relatively high serologic titer. Apparently serologic reactions of high titer in isolated instances can be unrelated to syphilis.

The results of the verification test in malaria are highly promising. The consistency with which positive serologic results in the absence of syphilis are accompanied by the general biologic type of reaction in this disease is striking. In view of the widespread distribution of malaria in different parts of the world, it is hoped that the verification technic will prove valuable in differentiating seropositive reactions due to malaria.

The implication that only one-third of the seropositive cases of leprosy are associated with syphilis seems to be epidemiologically reasonable. Extensive studies will have to be carried out with the verification test in leprosy before it will be possible to draw a definite conclusion as to its value in detecting the presence or absence of syphilis in such cases.

Effect of temperature on Kahn reaction.

IV. With serologically negative sera in the absence of syphilis. R. L. Kahn, E. B. McDermott and S. Marcus. *Am. J. Syph., Gonorr. & Ven. Dis., St. Louis*, 25: 173-178, Mar. 1941.

Certain serologically negative nonsyphilitic serums, whether from lower animals or human beings, when examined with the Kahn test under special conditions at 37° and 1° C., respectively, showed precipitation at 1° C. and little or no precipitation at 37° C. This kind of precipitation is a general biologic type of reaction. The reaction is relatively widespread among lower animals under apparently normal conditions and among human beings largely under pathologic conditions.

A total of 119 animal serums were examined with the verification test. The numbers of serums from each species which gave the general biologic reaction were as follows: Of 30 hog serums tested, 23 gave the reaction; of 35 rabbit serums, 16; and of 54 chicken serums, 27. Thus, 66 of 119 serologically negative animal

serums gave the general biologic type of reaction with the verification test. A total of 43 gave negative reactions. The authors state that unpublished data indicate that the number of animal serums giving negative verification reactions can be further reduced by the use of antigens more sensitive than standard Kahn antigen. It thus appears that animal serums, serologically negative with a diagnostic test, possess an inherent property of giving the general biologic type of serologic reaction.

Of 25 serologically negative serums from persons with malaria, 15 showed the general biologic type of reaction. After inoculation with malaria most of these nonsyphilitic persons gave, for limited periods, positive serologic reactions. However, after they began to give negative serologic reactions again, they showed the general biologic type of reaction with the verification test for varying intervals.

Of 25 serums from serologically negative leprosy patients, 13 gave the general biologic reaction with the verification test.

Of 440 Kahn-negative serums from routine examinations of the University of Michigan Hospital, 16 gave the general biologic reaction.

The authors believe it is possible that serologically negative persons giving the general biologic type of reaction are "potential carriers" of serologically positive reactions. One seronegative person who gave a general biologic reaction recently became seropositive during a febrile state and seronegative again during convalescence. Obviously, large numbers of seronegative persons will have to be tested with the verification test before it will be possible to establish that "carriers" of the general biologic type of reaction are "potential carriers" of false positive serologic reactions.

Some hitherto unrecognized excretion products of sulfapyridine and their relation to urolithiasis. John V. Scudi and Harry J. Robinson. *Am. J. Sc. (Proc. Physiol. Soc. of Philadelphia)*, Philadelphia, 201: 310, February 1941.

The mechanism of the urinary elimination of sulfapyridine is more complex than has been postulated before. A monohydroxyl derivative of sulfapyridine and its water-soluble glucuronide have been isolated from dog urine (Scudi, *Science* 91, 486, 1940). These products are ordinarily measured by diazotization procedures as "free" or "unchanged" sulfapyridine.

The formation and excretion of the products have been studied in the rat by Scudi and Robinson. Following the administration of the drug there was an increased urinary output of glucuronic acid which indicated that as much as 40 percent of the "free" sulfapyridine was present as the highly soluble glucuronide. This was confirmed by a study of the ratio of "free" sulfapyridine to acetylsulfapyridine, and a quantitative determination of the urinary hydroxysulfapyridine.

The excretion of a part of the drug in its soluble form is important in the etiology of acetylsulfapyridine urolithiasis. If the body is deprived of the mechanism whereby this soluble product is formed, the body must detoxicate and eliminate larger amounts of the drug in some other fashion. Following liver damage induced by phosphorus poisoning, the glucuronic acid output is no longer augmented by the administration of sulfapyridine. The production of the insoluble acetylsulfapyridine is not depressed.

Thus, three injections of phosphorus produced a 60-percent incidence of uroliths, whereas a control series of rats showed only a 10-percent incidence of stones at the sulfapyridine dose level studied.

preliminary studies in man (Scudi, Fish and Bullova, Science, 89: 516, 1949) indicate that man and the rat employ the same mechanism for the excretion of sulfapyridine. Thus, liver function should be considered in the etiology of acetylsulfapyridine urolithiasis.

PUBLIC HEALTH ADMINISTRATION

venereal prophylaxis. Editorial. Minnesota Med., Minneapolis, 24: 119-120, Feb. 1941.

In his autobiography, Hugh Young tells in intimate details of the way in which, for the first time in the history of warfare, a serious and effective attempt was made to control the incidence of venereal disease among the troops. It is a fascinating story of careful planning by a master and backed by competent authority. Hugh Young has done many things of importance in his long and useful life, but nothing he has ever accomplished bears comparison, for far-reaching benefit, to his skill and persistence in carrying out his ideas in the prevention of venereal disease. It furnishes an example for the whole civilized world of what could be done by carefully applied scientific knowledge properly enforced.

Abstract: Venereal diseases. J. Indiana Med. A., Indianapolis, 34: 140, Mar. 1941.

A cooperative attack on venereal disease by employers and employees is essential for the conservation of the national defense labor force, Surgeon A. J. Aselmeyer of the U. S. Public Health Service, called a joint meeting of health and civic groups in York, Pennsylvania, January 31, 1941.

He summarized the industrial losses of venereal disease as:

- 1. Lowered efficiency of the infected worker who neglects treatment.
- 2. Damage to equipment by workers whose infection has affected vital organs.

3. Production interruptions through replacement of these workers.

4. Workmen's compensation for well employees who may be injured in accidents caused by the infected worker.

5. Growing taxes to pay for infected workers who become public charges.

Aselmeyer said that defense against venereal disease begins on the home front. He called for diagnosis and treatment of infected persons, contact-tracing, and educational activities. The problem should be attacked by the community as a whole under the leadership of the city health department, the local medical society, and civic organizations, with the cooperation of the State and Federal public health authorities.

He said that there should be no special concern for the working capacity of an employee with a venereal disease as long as the employee is brought under regular treatment before he reaches the stages producing disability. The danger of infecting other employees is nil as long as treatment is secured regularly until the disease is cured.

Discharge of the infected worker borrows trouble for the community and the industry. In the long run such cases are reflected in higher relief and tax loads.

Both National and local leaders of the Congress of Industrial Organizations and the American Federation of Labor have endorsed the venereal disease program, but they insist on proper safeguards to prevent discrimination against infected workers. Cooperation will solve this problem. If the employers as civic leaders in the community, and their workers and families as members of the community, will unite in an attack on venereal diseases for the good of both, there need be no fear of discrimination.

Factors affecting the results of contact investigation in the syphilis clinic of the Johns Hopkins Hospital. Robert Dyar and Nobel W. Guthrie. Am. J. Syph., Gonorr. & Ven. Dis., St. Louis, 25: 215-224, Mar. 1941.

Syphilis control methods should aim to prevent (a) the spread of the disease

to healthy persons and (b) the development of late disabling lesions among persons already infected. In accomplishing the first objective, the prompt discovery and treatment of persons with infectious syphilis is essential in order to shorten the average duration of the infectious period. If the second objective is to be attained, it is important to discover persons with untreated syphilis regardless of whether or not they are potential sources of infection in the community.

In a previous report from the syphilis clinic of the Johns Hopkins Hospital, written by Turner, Gelperin and Enright (*Am. J. Pub. Health*, 29: 768, 1939), the results of the epidemiologic investigations of the contacts of 247 patients with primary or secondary syphilis were reported, and a method of analyzing data of this type was proposed. In this group, when only cases of syphilis not previously known were considered, for every 100 cases of primary or secondary syphilis admitted to the clinic voluntarily, 30 cases of infectious syphilis and 16 cases of latent syphilis were discovered among the contacts of the original patients. In addition, 24 contact cases already under medical care for syphilis were found for every 100 original cases.

In the present report, the authors present briefly the results of contact investigation obtained during the one-year interval subsequent to the period covered by the earlier report, and they discuss certain factors influencing these results and their interpretation.

The authors report that the investigation of the contacts of 133 cases of infectious syphilis led to the discovery of 72 previously unrecognized cases of syphilis. Forty-two of these were cases of primary or secondary syphilis (a ratio of infectious contact cases to original cases of 32:100). There were, in addition, 69 previously known cases of syphilis among the contacts named (52 per 100 original cases). Fifty-two of the contacts examined did not have syphilis (a ratio of 39 per 100 original cases).

Compared with the earlier study, there was an increase in the average number of contacts named and an increase in the proportion of contacts examined in the original case. This was not accompanied by an increase in the proportion of infectious contact cases or in the proportion of total new cases of syphilis covered.

Of all infectious contact cases discovered, 29 percent were under medical observation within 1 week following admission of the original case, and 67 percent within 1 month.

Examination of the contacts of cases of latent syphilis in colored males and females less than 25 years of age revealed only 1 infectious and 5 latent cases of syphilis. The ratio of infectious contacts discovered to 100 original cases is 13 times as great for original infectious cases as for original latent cases.

During the period covered by this study, a more intensive investigation of the contacts of each original case was conducted than during the first study. The result was that a much larger number of contacts were named. Many of these contacts were poorly identified, and that follow-up of this group with approximately the same amount of social service effort per contact named led to the examination of a lower proportion of named contacts than in the previous study. Moreover, the number of social service visits per new case discovered was almost twice as great during the second period as it was during the first. The findings indicate that during the second period a point was reached at which increasing social service effort yielded diminishing returns.

Syphilis control program in a minority community. R. L. Stewart. *J. M. A. A.* Alabama, Montgomery, 10: 265-268, Feb. 1941.

Strenuous physical labor such as coal mining is apt to cause valvular heart disease, aortic dilatation, or aneurysm in persons with latent syphilis.

The president of the Alabama Fuel and Iron Company realized the masked physical hazards and the economic waste caused by syphilis. He suspected a high percentage of syphilis among Negro employees of the company and proposed a compulsory antisyphilitic program to be conducted by the company doctors in order to find and treat adequately all patients with syphilis in the community. An educational program was launched, with officials of the company, doctors, and organized groups in the community cooperating. The subject of syphilis was given a prominent place on several programs of both white and Negro welfare societies. Free lectures, pamphlets, and motion pictures on syphilis from the State health department were presented. When the attitude of the community had been molded to support such a program, a serologic survey of the population was begun.

About 75 percent of the persons in the community were Negroes. Each family paid a nominal sum each month for medical care. Without any additional expense the old employees and their families were given a thorough physical examination which included a blood serologic test for syphilis. Since that time such a blood test has been made as part of the routine preemployment examination. Those employees with positive tests were not discharged but were required to begin treatment immediately. The survey extended from the fall of 1937 to January 1940 with the following results: Of 1,535 Negroes tested, 228 (14.9 percent) had positive tests. Of 663 white persons tested, 5 (0.75 percent) had positive tests. Of the total number (2,198) tested, therefore, 10.6 percent had positive tests.

Twenty-seven percent of those with positive tests had "early" syphilis and 71 percent had "late" syphilis. Those persons with positive tests in the absence of any history of previous infection were considered to have "late" syphilis. Those who gave a history of recent infection were considered to have "early" syphilis.

The names of Negro persons with positive tests were given to their mine foremen. These Negro patients were then called to the office where the consequences of the disease were explained, and the importance of treatment was stressed. These patients were each given a card with 52 spaces representing each week in the year. When the weekly treatment was administered, the card was signed by the physician and checked by the foreman when the employee reported for work. Employees whose cards failed to show the doctor's signature for the past week were not allowed to work until they had obtained a written order from the doctor to return to work. The names of the five white patients were not given to their mine foremen.

Routine treatment consisted of 18 months of continuous therapy, alternating 10 intravenous injections of neoarsphenamine with 10 intramuscular injections of bismuth at weekly intervals. The treatment varied with the individual patient and especially with those showing intolerance to the drugs.

Patients who refused treatment were advised to leave the community, and 6 of them did so. More rigid rules should be applied to such persons. Eighty-seven left the community at different times for various reasons: 51 were taking treatment in January 1940; 89 completed 18 months of continuous treatment (79 percent of these had negative blood tests at the end of treatment).

Cooperation from the patients was, on the whole, very good. Objections were based on the dread of the needle prick, soreness at the site of the hip injection, and a generalized rash in a few cases. The percentage of drug reactions was small.

Epidemiology in the control of syphilis.

Bull. Genitoinfect. Dis., Boston, 4: 3-4, Feb. 1941.

The records of the Massachusetts Department of Public Health furnish the following study in epidemiology: Case 1, a 23-year-old girl, was interviewed by the department's follow-up nurse for her

lapse in treatments for gonorrhea. The nurse noticed a rash on the hands of the married woman who lived with the patient, and the husband was found to have a sore throat. Examination confirmed the nurse's suspicion that this couple had syphilis.

Case I named case II (a 30-year-old man) as the probable source of her infection with gonorrhea. Case II was found to have secondary syphilis, and case I, by this time, had developed a syphilitic rash and positive serologic reactions. The reconstruction of the path of infection in these four cases of early syphilis was not difficult, for case II had had intercourse with case I and also the married friend, and she, in turn, had infected her husband.

In tracing the infection of case II, case III was found, who named 7 male sexual

contacts. The contacts were all brought to medical attention. Case A was finally brought to medical attention in Connecticut; case B was normal; case C had penile lesion and admitted exposing his "girl friend" but she was found to be free from infection. Cases D and E showed no infection. Case F showed primary syphilis but there were no contacts. Examination of case G revealed that he, his wife, and their 6-month-old child were all infected.

Therefore, because one physician had requested assistance of an epidemiologist in having a patient return for treatment of gonorrhea, 10 cases of early syphilis were discovered. The investigation involved the search for, interview and examination of 15 different individuals. Wherever gonorrhea is found, the possibility of syphilis must be considered.



Preservation of the Gonococcus in Frozen Urines and Broth

MORRIS S. WORTMAN, M. S., AXEL GRONAU, M. D.,
ROGERS DEAKIN, M. D., and FRANCES LOVE, A. B.

RATIONAL therapy and successful control of gonococcal infections depend to a large extent on the accuracy of the diagnostic method. The superiority of the culture over the smear in the diagnosis of gonorrhea is now an established fact (2, 3, 4).

Facilities for the cultural method frequently are accessible in the larger cities but are usually lacking in smaller communities and rural districts. Under these circumstances it would appear that progress in the control of gonorrhea would be promoted if specimens taken from patients with gonorrhea could be transported to a district or central laboratory for cultural diagnosis as is common today for stool specimens in the case of enteric infections. The gonococcus is notorious, however, for its fastidiousness and its great susceptibility to even slight changes in its environment. This is probably the reason that no satisfactory method, successful as a routine measure for the preservation of gonorrheal specimens during transport, has yet been devised.

In the search for a suitable method, one of us (Wortman) suggested that the specimens might be frozen rapidly in a mixture of dry ice and 95 percent ethyl alcohol and then preserved in a frozen state in a container packed with dry ice. A few preliminary and successful experiments conducted by Wortman and Love with the bacteriologic work done by Gronau encouraged us to investigate the

feasibility of this method on a somewhat larger scale.

METHODS

The routine procedure for culturing gonorrheal specimens in this laboratory has been described in an earlier paper (4) and only brief reference to this procedure will be made here:

Routine method.—The urethral discharge of male patients with gonorrhea was collected on a sterile swab which was then immersed in a serologic test tube containing 1.5 cc. of infusion broth. Subsequently the specimen was plated out on a chocolate agar plate. If there was no discharge, the first portion of the urine was collected in a sterile centrifuge tube. The sediment was taken up on a swab after centrifugation and transferred into a broth tube. A culture was then made as stated above.

In female patients the cervix was exposed by means of a speculum, avoiding the use of lubricants. A specimen was taken from the urethra and cervix with a swab which was then immersed in a broth tube and later plated out as described.

Freezing method.—(A) BROTHS. A routine culture was made from the discharge in both male and female patients and then the swab was placed back into the broth tube. The broth tube then was immersed in the freezing mixture of dry ice and alcohol (temperature about -72° C). Freezing occurred in about 15 to 20 seconds. The specimens were transferred when frozen to a thermos bottle containing dry ice. (B) URINES. Urines collected in sterile 15 cc. centrifuge tubes were frozen by immersing the tubes in the freezing mixture. Freezing

From the Department of Bacteriology, Washington University, and the Washington University Clinics, St. Louis, Missouri, in cooperation with the Missouri State Board of Health.

occurred in about 1½ to 2 minutes. The tubes were transferred after freezing to a thermos bottle containing dry ice.¹

Both the discharge in the broth tube and the first portion of the urine (containing suspended discharge) from most of the male patients were frozen. This was done to compare the influence of these two environments on the survival of gonococci in the specimens.

In the cases in which there was no discharge the first portion of the urine was divided into two parts, one to be used for routine culturing, the other for freezing.

Specimens were kept in a frozen state between 24 and 55 hours before being cultured. They were thawed by immersion in water of room temperature and cultured as described above. All cultures were incubated in an atmosphere of 10 percent carbon dioxide at a temperature of 36° C. It is essential that the chocolate agar plates used for the culture of frozen specimens be very fresh, not older than 1 or 2 days at the most. Care must be taken, also, to insure that specimens will remain frozen until they are ready for culturing. It might be advisable to extend incubation of the plates to 3 days instead of the usual 2, since in a number of instances the lag-period of growth apparently was lengthened.

RESULTS

Males.—The specimens of 69 male patients were shown to contain gonococci by routine culture. Portions of these same specimens were subjected to the freezing procedure. The frozen specimens were thawed 24 hours later (in some instances as much as 48 to 55 hours later) and plated out as described. Gonococci were cultured in routine fashion from 62 of the 69 male patients. In 48 of these 62 patients the discharge in the broth tube, as well as the first portion of the patient's urine, were frozen; in the remaining 14 patients, only discharge in the broth tube was frozen.

¹The 95-percent alcohol used in the freezing may be used repeatedly until diluted too much by the absorption of moisture.

The cultures of 61 of the 62 frozen discharges were positive while only 42 failed to grow. The cultures of 42 the 48 frozen urines were positive, 6 were negative. Of these 6 failures occurred on the same day.

There were six patients who had discharge when the urine was subjected to freezing. The cultures of three were positive, and three were negative.

One patient had an acute gonococcal prostatitis. The prostatic fluid obtained after massage was frozen in the usual manner and cultured 24 hours later. The culture was positive.

Females.—The cervical specimens of female patients were shown to contain gonococci by routine culture; these cervical specimens in the broth tubes were frozen at the same time that the routine culture was made. The cultures of 15 of the 16 frozen specimens were positive while 2 were negative.

A swab of the cervical exudate from one female patient was placed in a syringe tube containing the patient's urine instead of broth. This was frozen in the usual manner and cultured 24 hours later. This culture was positive.

A higher percentage of the cultures of the frozen specimens probably would have been positive if it had not been necessary to use the same swab twice—for routine culture first and then a second time for the freezing procedure. Much of the discharge collected on the swabs was removed when they were used at the first time for the inoculation of the routine plates, and only what was left on the swabs could be used for the freezing experiments.

DISCUSSION

This series of experiments is limited, and we are aware that no definite conclusions can be reached yet as to the practicability of the freezing method for preserving gonococci in specimens during transport. The results obtained so far with this method, however, seem to justify an investigation on a larger scale than is possible in a single laboratory.

the freezing method might be found to be diagnostic help particularly in the diagnosis of gonorrhea in female patients, where the microscopic examination of smears frequently fails.

SUMMARY

A method has been described for preserving gonorrheal specimens during the time which might be required for transport of a suspected exudate to a distant laboratory for culture.

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Treatment of Gonorrhea in the Male with the Sulfonamides

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SULFANILAMIDE was introduced in the treatment of gonorrhea in 1936. The first two years were devoted largely to experimentation and research into its efficiency and toxicity, whereas since then much time has been devoted to a search for improvements on the original compound and the standardization and rationalization of its use. Nothing of importance has been noted during the earlier period to alter conclusions gained in the first 2 years insofar as the use of sulfanilamide itself is concerned. Two other compounds have been added to the sulfonamide series which seem, on the basis of published reports and from our own experiences, to offer greater therapeutic efficiency and lesser degrees of toxicity. These drugs are sulfapyridine and sulfathiazole.

More than 5,000 males with gonorrhea have been treated at the Los Angeles City Health Department with some form of sulfonamide therapy during the past 5 years. Our first report in 1938 published by the *Journal of the American Medical Association*, concerned itself with an analysis of 1,620 cases. The present paper relates primarily to 792 proven and cases selected from a group of 2,222

cases because they remained under our supervision a sufficient length of time to enable us to perform certain tests of cure, including prostatic cultures. The remaining 1,430 cases had similar therapy, but, for various reasons, did not complete the tests of cure, including cultures.

The results obtained in the total of 2,222 cases under treatment with sulfonamides between December 15, 1938 and July 1, 1940 are as follows:

Tested cures.....	792
Presumptive cures.....	447
Symptoms last visit.....	159
Observed less than 5 days.....	824
Total.....	2,222

The first group of 792 tested cures is the basis for the analysis in figures 1, 2, 3, and 4, while the combined 447 and 159 cases in the two succeeding groups form the basis for figure 5. In the addendum is indicated the outcome in 356 additional cases which were treated with sulfathiazole and which came under treatment between July 1, 1940 and October 15, 1940.

The optimum dosage for sulfanilamide has been fairly well established. With few exceptions, the following dosage

schedule has been followed in this series: 20 grains 4 times daily for 2 days, 15 grains 4 times daily for 5 days, and 10 grains 4 times daily for 2 days. The optimum dosage for sulfapyridine and sulfathiazole has not been as definitely established. The dosage for these drugs, as used in this series, was 4½ grams divided into three doses for the first and second days, followed by 3 grams divided into three doses for the next 4 days. This period may be extended to 10 or 14 days. A second course was usually prescribed for recurrent cases. The initial dose should be large. The use of the maximum tolerable dosage might be indicated in a patient with severe metastatic extensions of the disease, such as arthritis, but similar amounts are not warranted in a simple urethritis where the only point at stake is the duration of the discharge. Practically all favorably influenced cases were

symptom-free during the first 24 hours of treatment. Figure 2 illustrates the comparative therapeutic efficiency of three sulfonamide compounds on the above-mentioned dosage schedule.

The side reactions vary in quantity and quality. Symptoms range from very mild or practically negligible ones to those that are very severe and sometimes fatal, showing involvement of practically all body systems separately or in various combinations. Sulfapyridine may exhibit a higher toxicity than sulfanilamide when used in the large doses necessary for the control of the pneumonias, but this is not true of the smaller doses advised in the treatment of gonorrhea. Mild gastro-intestinal upset appears most frequently with the use of sulfapyridine. Other disturbing symptoms such as dizziness, dyspnea, paresthesias, chill-fever-like syndromes, accompanying sulfanilamide are less frequent in sulfapyridine therapy. We met with practically no undesirable side reactions in the use of sulfathiazole, though such reactions are definitely a possibility. Oliguria, hematuria, loin pain, and anuria appear occasionally with the use of sulfapyridine. Our series was accompanied by an astonishingly low frequency of severe side reactions. Figure 3 illustrates this point. We might add here, that 50 mg. of nicotinic acid was prescribed 30 to 60 minutes prior to each dose of sulfapyridine. This, we believe, accounts for the low incidence in our series of gastro-intestinal upsets. No such precautions were resorted to in the use of sulfathiazole.

The sulfonamides are excreted by the kidneys. Inadequate renal function due to Bright's disease or obstructive uropathies would, perhaps, result in dangerous blood levels if the usual dosage schedules were followed. Dosage in patients with renal disease must, therefore, be regulated by blood level determinations. Fortunately, since gonorrheal infections usually occur in youths and otherwise healthy individuals, such lesions are rare. Because of lack of facilities, complete blood counts and hemoglobin estimations were not done routinely except in those cases

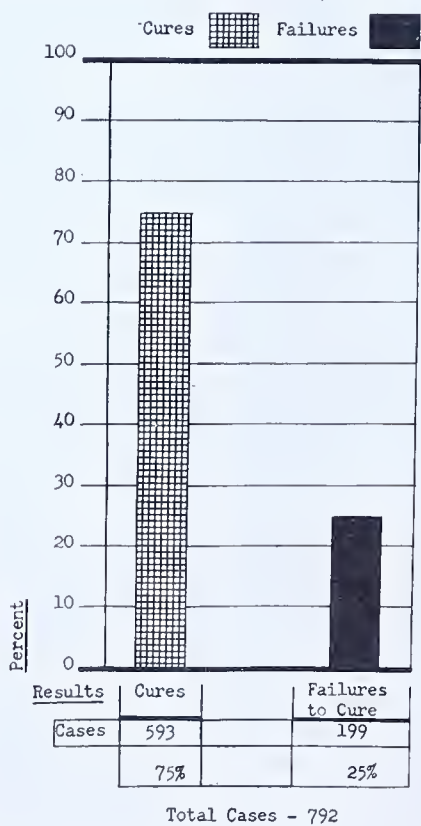


FIGURE 1.—Proportion of cures and failures after sulfonamides alone among 792 male patients cured of gonorrhea (Los Angeles City Health Department, 1939-1940).

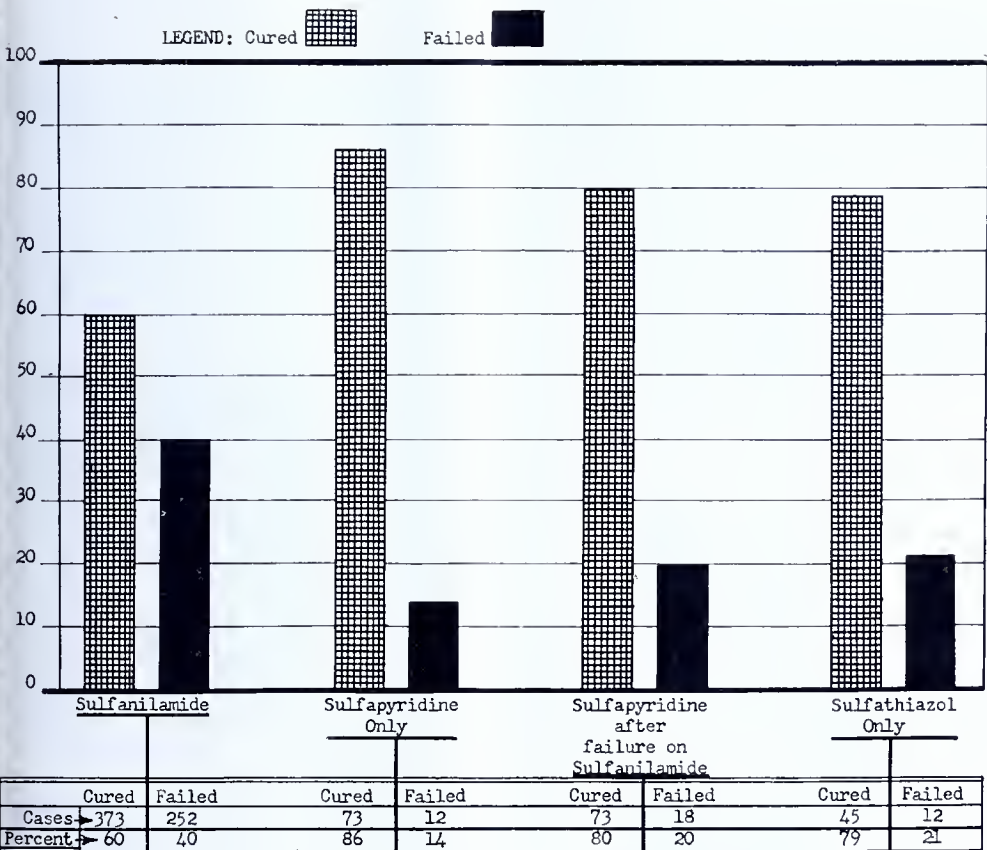


FIGURE 2.—Proportion of cures and failures after each of the indicated types of treatment (in 25 cases the type of sulfonamide used was not known) among 792 male patients cured of gonorrhea (Los Angeles City Health Department, 1939-1940).

representing signs indicative of a toxic state. In these the urine was also examined.

In determining the classification of side reactions as they are reported in figure 1 all reactions resulting in the discontinuance of the drug, regardless of severity, are classed as severe side reactions. The mild reactions include only those cases in which the subjective complaint could be confirmed by at least one objective sign such as pallor, dyspnea, dark-colored urine, and cyanosis. In no instance did any of the cases under observation in this series require hospitalization, nor was there any doubt as to the outcome of the toxic state in question.

Figure 4 shows an analysis of the various intervals between admission and dismissal and includes such items as duration of sulfonamide therapy, intervals

between cessation of symptoms and start of cure tests, and intervals extended to culture and to dismissal of patient. Of interest also is the ratio indicated by the figures for syphilis which remained about the same throughout the series.

On the basis of the 792 cases followed until cured plus the 606 cases in figure 5 which were observed 5 days or more, sulfathiazole would appear to be the drug of choice. Its therapeutic efficiency on the basis of these 1,398 cases appears to be greater than sulfanilamide, but slightly less than sulfapyridine, and on the basis of the 792 cases followed until cured its toxicity appears to be lower than that of either of these other drugs.

Management of gonorrhea in the male.—Diagnosis is based upon a positive smear (using the Gram stain) and careful examination of the patient to determine

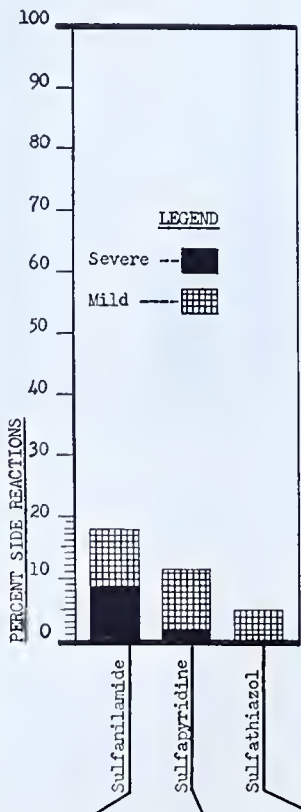
the extent and severity of the infection. The two-glass test is used in all cases. An attempt is made to treat every patient on his first visit to the clinic. Sulfathiazole is the drug presently used with dosage as recommended above. Oral and printed instructions relating to the use of drug, hygiene, and diet are given the pa-

ment during the first 10 days of his disease. If toxic symptoms are present, the drug is either discontinued or the dosage reduced, depending on the severity of the symptoms. Blood counts and urine analyses are made on all such cases. The use of anterior urethral instillations of mild silver proteinate or neutral acriflavine is optional. At the clinic, mild solutions (1:6,000) of potassium permanganate are used. The use of gonococcal vaccine to stimulate antigenic response is also optional. In anteroposterior infection the prostate gland is massaged fairly vigorously 48 to 72 hours after starting sulfonamides. The patient must be honest in taking drugs as prescribed to insure the safety of this procedure. The massage is followed by deep irrigations with warm potassium permanganate solution. In obstinate prostatic infection the gland may be massaged every other day. A careful search should be made for abscess and nondraining foci. These must be opened and drained as indicated. In exceptionally stubborn cases a change may be made to 1:2,500 silver nitrate anterior irrigation daily and 1:500 solution of silver nitrate instilled posteriorly with a silicon woven acorn-tip posterior urethral instillator.

Tests of cure.—There is a definite danger of too early dismissal of the patient due to the early clearance of symptoms. This naturally tends toward relapse and latency in infection and increases the hazards of the carrier problem. This may be avoided in great part by close adherence to the tests for cure. Our routine is as follows:

1. Routine massage of the prostate gland one week after abatement of all clinical signs of gonorrhea. This should be repeated if the secretion obtained contains more than 10 pus cells per high power field or if the Gram stain reveals gonococci.

2. Four days later, sounds, beginning with a size 20, are passed into the posterior urethra.



	Sulfanilamide		Sulfapyridine		Sulfathiazole	
	No.	%	No.	%	No.	%
Cases	625	100.0	176	100.0	57	100.0
Mild Reactions	54	8.6	18	10.2	3	5.0
Severe Reactions	60	9.6	3	1.7	0	0.0
Total (Reactions)	114	18.2	21	11.9	3	5.0

FIGURE 3.—Proportion of patients having side reactions after treatment with the sulfonamide indicated (in 25 cases the type of sulfonamide was unknown), of 792 male patients cured of gonorrhea (Los Angeles City Health Department, 1939–1940).

tient. He is urged to return to the clinic at least three times each week at which time he is questioned and examined for untoward signs and is given local treat-

	LONGEST	SHORTEST	MEAN	MOST	LEAST	MEAN	RECURRENCES AND RE-INFECTIONS
Days duration of Sulfonamide treatment	30	2	8.2				
Days symptom free to 1st cure test	166	1	10.5				
Days from cessation of drug to culture	166	1	14.9				
Number of visits for observation or treatment				57	6	16.5	
Number of days from admission to dismissal				224	19	59.3	
Number of recurrences after neg. culture							2 cases - no reliable reinfection data
Number of re-infections							30 cases*- highly probable from history and exposure data.
							* (If included in this series are classified as new cases)

Syphilis diagnosed while under G. C. treatment	34
Syphilis diagnosed prior to G. C. treatment	31
Admitted and dismissed (Serology negative)	727
Total.....	792

FIGURE 4.—Recurrences, reinfections, and time-interval analysis of a group of 792 male patients treated with sulfonamides and cured of gonorrhea.

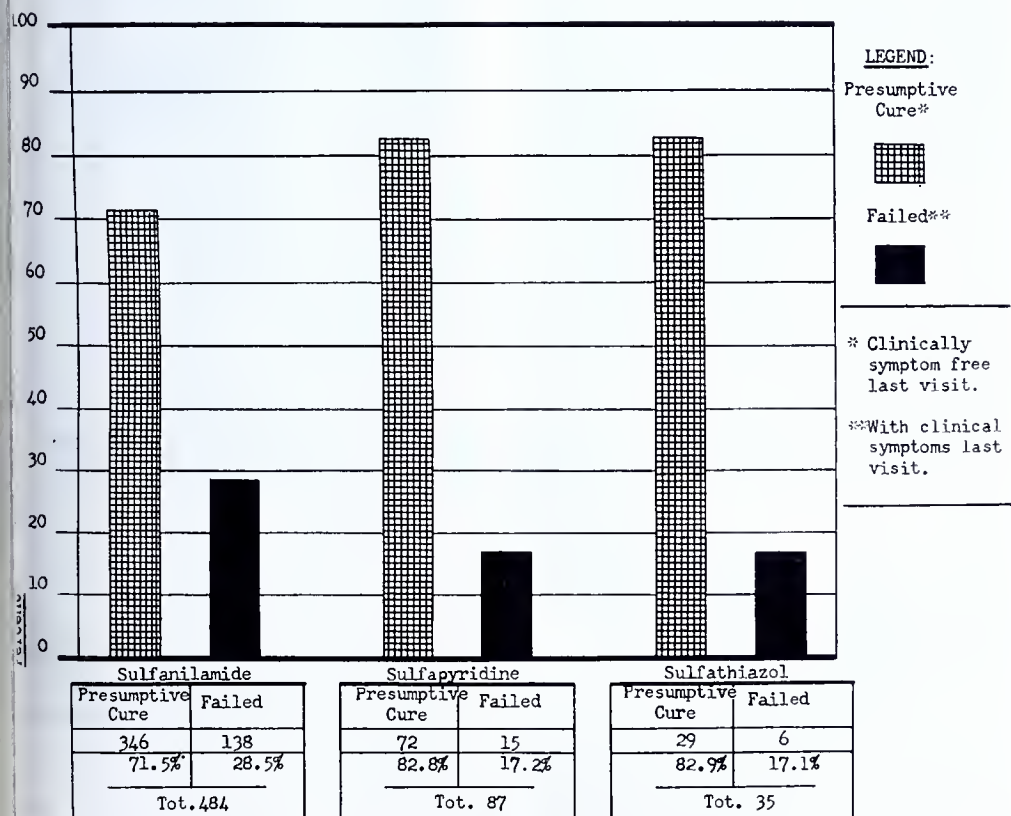


FIGURE 5.—Proportion of patients presumably cured and patients not cured in a group of 606 male patients treated with the sulfonamide indicated and given incomplete tests of cure observed for 5 days or more.

3. One week later, if no symptoms have developed during the interim, the prostate is once again massaged before the patient voids. A few drops of the prostatic fluid are collected in a culture tube of broth and cultured. One negative culture, and 3 weeks of observation, during which period there must be no recurrence of clinical signs or symptoms, are required before a patient is dismissed as cured. If facilities for culture are not present, it is wise to extend the period of observation to a 3-month period.

General rules followed in the management of gonorrhea in the male.—Under no circumstances shall any cotton, cloth, bags, or paper of any nature be placed over the end of or around the penis. This ban may include the tight-fitting jock strap and the jockey-shorts. Inasmuch as discharge is, in general, promptly controlled and as the sulfonamides do not work satisfactorily in the presence of obstructions to free drainage, soiling of the patient's clothing should be tolerated temporarily. We have no objection to the use of the so-called "butterfly" dressing. Diet is of secondary importance. Any food which is irritating to the mouth will probably find a similar response in the urethra. Rest, continence, and abstinence are always indicated.

ADDENDUM

Results of Sulfathiazole Therapy in 38 Cases of Gonorrhea in Men, Los Angeles City Health Department, July 1, 1940 to October 15, 1940

	Numb of cas
Tested cures:	
Cultures negative-----	18
No cultures made-----	4
Symptomatic cures, no cultures or other tests made-----	4
Improved but not cured-----	2
No results, failures-----	2
Toxic reactions from drug:	
Mild -----	1
Severe -----	1
Treated previously with sulfanil- amide unsuccessfully, cured with sulfathiazole-----	67
Treated previously with sulfapyri- dine unsuccessfully, cured with sulfathiazole -----	7
Treated previously with both sulf- anilamide and sulfapyridine un- successfully, cured with sulfa- thiazole-----	6
Failed on all sulfonamides-----	8
Required two or more courses of sulfathiazole for cure-----	2
Treated with sulfathiazole but ob- served less than 5 days-----	
Total -----	31

Case-Finding with Gonorrhea Patients in a Clinic for Venereal Diseases

EDGAR C. BALDOCK, B. A. (New Zealand)¹

MR. B. COMES into the social worker's office after having seen the doctor. His infection has been diagnosed as gonorrhea. He has just been advised of this and given the first of his treatment. He is still distressed and worried and doubtless feels ashamed of his infection. His main thought is to take the advice of the physician and to carry out the treatment as advised with a sincere resolution to

get well as speedily as possible. However, his infection is a communicable one. He has contracted it from another person. Because of the symptomless incubation period he may have already infected a third person. The preservation of the public health necessitates the obtaining of information concerning contacts. If the spread of gonorrhea is to be lessened and eventually halted, this information must be obtained as soon as possible. But the method of infection is by intimate personal contact. For years venereal di-

¹ Graduate work at State University of Iowa and Washington University, St. Louis.

and sex have been taboo. The patient, sharing the attitudes which make the suppression of all information dealing with these two subjects, is little inclined to disclose his personal knowledge concerning his particular situation. There then, is a difficult and delicate situation. It is part of the work of the interviewer to cope with it.

Reasons for case finding.—Why should the delicate situation above-mentioned concern the public health worker? The main reason is, of course, the protection of the health of the public. Could we allow unsuspecting innocent persons to suffer? What about the health of the wife whose husband has "stepped out." Should a small sister contract vulvovaginitis because her youthful brother did not wish to disclose to his parents that he had made a mistake." These are some of the reasons why the social worker in the venereal disease clinic must trace the patient's contacts.

There is a further reason, namely, the discovery of the sources of infection. Here we are confronted by a boomerang situation. The patient must be interviewed in case he has had contact with a prostitute, because she can be the source of so much disease. We must control prostitution so that in the future there will be need for less and less contact examination. Prostitution is the evil smell in the swamp in which the public health worker bogs down. It must be drained and cleared. In the meantime, contact examination may help in some measure to do this.

Obstacles encountered in contact interviewing.—As has already been stated, interviewing for contacts is a delicate matter. Every social worker knows that the client seeks his assistance because of some difficulty which, for the moment, appears to be overwhelming. In the case of the patient in the venereal disease clinic does not even have the option of seeking advice or help. He finds himself facing a person whose aim is to obtain from him details of a most intimate nature. It may not be out of place to mention at this point that in the clinic where the

writer works, the patient is seen on his first visit, in the first instance, by a social worker. It is recognized that the patient comes to the clinic because he has an infection concerning which he is greatly perturbed. He comes seeking a cure. Yet, despite this fact, it is felt that a few moments spent with the worker, who later carries out the contact interview, will result in cooperation and in the prevention of future delinquency from treatment. It is the first step in the establishment of rapport between patient and worker.

When some of the difficulties which arise during the contact interview are considered, the effect on the patient of the period of waiting prior to examination should not be overlooked. Patients fall into conversation with one another. All types of men are to be seen in the waiting room. We find the callow youth hiding his distress under a cloak of bravado, trying to give the impression that he knows all about the venereal diseases but inwardly craving for knowledge. Perhaps next to him sits a "repeater," we call him this for want of a better word. His chart reads, "Admitted —. Discharged —. Readmitted —. Discharged —." The possible trend of the conversation may easily be imagined.

During this period of waiting the situation is in process of being defined for the new patient. Tennyson wrote in *Ulysses*, "I am part of all that I have met." It is here that the value of the preliminary interview with the social worker becomes patent. It can help in the defining process. It is possible that from this period of waiting later difficulties in the contact examination may derive. The youth sitting next to the patient who "has his woman" may lend a willing ear to his stories. Because this patient would not dream of disclosing the name of "his woman" he may influence the young man to attempt to act similarly. But this is but one of the difficulties which the interviewer may encounter. Let us list a few.

Resistance to the interviewer frequently arises out of a feeling of guilt

or shame. Pelouze has brought out this fact. He has shown how the patient passes through several phases until finally he loses this feeling. How often are these words heard from the new patient, "This will never happen to me again. I am ashamed of myself." Dr. William Malamud, formerly Assistant Director, Iowa State Psychopathic Hospital, in his "Outlines of General Psychopathology" draws attention to the fact that when there is a feeling of guilt present it is frequently associated with depression. This appears to be particularly true of many gonorrhea patients. These factors often create a barrier which the interviewer must hurdle.

Some patients possess a feeling of honor, an honorable but misplaced idea that the sexual partner must be protected. I have noted that even when the source of infection is a prostitute, the patient is reluctant to disclose identifying information. It may not be untrue to state that some patients regard prostitutes with what may almost be termed affection. This refusal to disclose information springs in part, no doubt, from the disinclination on the part of the patient to get the girl into trouble with the police.

One difficulty arises from the well-known fact that liquor and the venereal diseases so often form part of the same picture. The patient in these cases cannot give information because his knowledge is insufficient. Doubtless some patients use this fact to enable them to escape giving information. Nevertheless there is little doubt that when the patient says "I was out on a binge the other night" he really was. Still, it is marvelous what information may finally be obtained from such a patient in a series of interviews.

Some patients resent the interview as an unwarranted interference with their private lives. It is possible that this feeling is bound up, to some extent, with the moral issue which the patient does not wish to face or acknowledge. This difficulty is closely allied to the next

which we may term, perhaps incorrectly "stubbornness."

I have met with surprisingly few cases of stubbornness. It is possible that conscious factors enter the situation. Some trait in the personality of the interviewer which may relate to a similar trait in a despised person, may be the cause. On occasions the patient may feel that he is in a subordinate position in the interview situation, despite the fact that this is not really the case. Sometimes this is associated with the desire to protect the girl. Of the few cases of stubbornness which I have encountered, it may be admitted that little success, in spite of changes of approach or of leaving the matter for a time, has been obtained. One case comes to mind, that of a patient who came into the office, sat down, commenced to strum his fingers on the desk and regarded the interviewer with a truculent stare. The situation suggests the influence of "the waiting room period" previously mentioned. Despite all efforts on the part, not only of the worker but of two physicians, to overcome this attitude, all the information which could be obtained was two names. Study of this type of patient with a view to the discovery of the causes of and treatment of such an attitude would prove of value. The fact that the trouble may lie with the interviewer is not disregarded.

Possible future marital difficulties may complicate the situation. The elderly man whose wife has for some time been frigid towards him, the husband whose wife has been away for a few days and who "picked up" a girl or who visited a house" with his friends are in considerable trepidation now that they are infected especially if the man has since had sexual relations with his wife. This type of patient usually is only too willing to give the name of the person from whom he contracted his infection. When the necessity for the examination of the wife is pointed out, the trouble begins.

The above are some of the difficulties and resistances which the interviewer encounters in the gonorrhea clinic. The

ly equally to the syphilitic patient. What may be done to counteract and overcome them?

Aids and methods.—Certain conditions are prerequisite to successful interview with patients in a venereal disease clinic and certain procedures are useful in dealing with these patients. Certain (what might be termed) physical conditions, should be present. Of these, privacy is probably the most urgent. More than once have I seen a patient glance apprehensively towards the door or glance before speaking. Should one of the reasons for any reason have to enter the clinic, the patient will in most cases cease talking, on occasions glancing towards the floor until the intruder has gone. When the patient feels that he can give intimate details without the fear of being overheard, he is more willing to cooperate with the interviewer.

Another very important prerequisite is certainty on the part of the patient that his mind is at rest concerning his infection and its treatment. If for any reason he is uncertain on any point, it is advisable to have him see the doctor in person. Assurance on this point means greater probability of cooperation with the social worker in contact examination. The attitude of the interviewer is extremely important. It may be stated at this point that the great proportion of the patients with gonorrhea have acquired it premaritally or extramaritally. When the patient realizes that the ethics of the situation are not in question, when he sees that the interviewer is considering his infection purely from the public health standpoint, then cooperation is more readily forthcoming.

The interviewer should link this attitude closely to the pronouncement that the information which the patient gives is absolutely confidential. When the patient realizes that there is no intention on the part of the social worker of disclosing what he says to outside agencies, he is usually willing to help. Allow the patient to see one of the consent forms which the clinic uses when it is desirable to acquaint a worker from an out-

side agency with facts concerning his infection frequently proves of value, even though the consent form applies to medical facts in most cases. It is an example of the educational principle that the concrete example is more effective than the abstract. It also illustrates the psychological fact that a person is reached more effectively through more than one sense and that most persons are influenced more through one of the senses than through the others.

The importance of "face-saving" should be realized. Most clients in their relationships with social workers have at one time or other the need for this escape. This applies particularly to work with patients in a venereal disease clinic. It should be recognized as basic that at the first interview, if the patient is under particular stress and strain, complete information should not be pressed for. Rather should he be allowed to depart with the feeling that if his attitude changes he is at liberty to see the interviewer at any time. In many cases the patient soon returns or telephones to give the required information. This principle would appear to contradict that which states that immediate follow-up of contacts is essential. Is it not better to wait a little while and finally be placed in possession of the necessary information which will enable the contact to be found, than to press and harry the patient until his cooperation is lost?

A further aid to interviewing is the realization on the part of the patient that the interviewer appreciates the social implications of the situation and is willing to aid him to cope with the problem.²

One very simple but extremely effective aid to interviewing is the contact diagram which illustrates by means of block figures and connecting lines how infection spreads from person to person. This appeal to the eye is extremely ef-

² For further consideration of this problem see the writer's condensed report in the June (1940) issue of the Bulletin of the Provincial Board of Health of British Columbia, "Some Social Effects of the Venereal Diseases."

fective. It may frequently alter the whole trend of the interview from a hesitating to a definitely cooperative stage.

The above illustrates in a simple way the elements in the contact-finding interview. In no form of interview would it appear that the saying "make haste slowly" is more applicable. Some patients find no difficulty in giving the required information in a few terse sentences, others must be permitted to take their time; some must be helped by skillful questioning, while others must be prodded.

These few thoughts, the result of experience, have been set down in the hope that others may benefit and in turn offer constructive suggestions. As A. C. Benson said in his essay, *The Criticism of Others*, "one of the nearest and simplest of duties is the perception of others' points of view, of sympathy, in no limited sense." He concludes, "that sympathy we can only gain through looking at humanity in its wholeness." If this point of view is not sufficiently perceptive, at least it may suggest efforts on the part of others more perceptive.

DIAGNOSIS

Diagnosis and treatment of the venereal diseases. Circular Letter No. 18. War Med., Chicago, 1: 247-266, Mar. 1941.

An outline of the use of chemotherapeutic agents in the treatment of infectious diseases and other infections as recommended by the Committee on Chemotherapeutic and Other Agents and its Subcommittee on Infectious Diseases of the Division of Medical Sciences, National Research Council, was published in Circular Letter No. 18, dated December 5, 1940. Circular Letter No. 18, containing an outline on the diagnosis and treatment of venereal diseases, records briefly the opinions and recommendations of that committee, as prepared by its Subcommittee on Venereal Diseases and approved by

the Committee on Chemotherapeutic and Other Agents.

Because of the rapid development of chemotherapeutic agents, it is likely that some of these recommendations will have to be modified from time to time. Certain measures other than chemotherapy are described where appropriate. These recommendations are published as a general guide for medical officers and are to be used at their discretion, with due consideration of all other factors which may be presented by each individual case. It is not intended that they should be used to the exclusion or neglect of other indicated therapeutic or nursing procedures.

Syphilis in old age. L. T. Hilliard and Brian H. Kirman. *J. Ment. Sc., London*, 87: 101-108, Jan. 1941.

Tooting Bec Hospital is the only hospital in England devoted entirely to senile dementia. The patients consist of "certified," or old patients with a chronic psychosis transferred from other mental hospitals, and "uncertified," or patients over the age of 70 when they became mentally ill and who are admitted directly to Tooting Bec. There are 2,300 beds at the hospital, and the average age of the patients is 73 years for men and 75 for women.

The blood of all male patients admitted during 1936, 1937, and 1938 (except for those who refused or who died before the investigation was carried out) was examined. Out of 701 patients, 69 (10 percent) had either a positive Wassermann and/or Meinicke reaction; 108 cases were not tested. A group of 100 cases with abnormal serums was then examined in more detail, including the spinal fluid. Among the 64 noncertified cases 8 (12 percent) had an abnormal cerebrospinal fluid finding; this is about 1.5 percent of the 520 noncertified patients admitted during this period.

There were 29 patients with a negative Wassermann test and a positive paralytic test as compared with 20 patients with both tests positive. It is not likely that the patients with the negative Wassermann

mann test had had treatment sufficient to render the Wassermann reaction negative. It is possible that these patients have had active syphilis but have undergone a spontaneous cure. The third possibility is that the positive Meinicke test alone does not necessarily signify syphilis, but some modification has taken place in old age which results in a positive Meinicke test.

Many of the patients showed signs which in younger persons might be taken as evidence of syphilis; in elderly people the interpretation of these signs is difficult. The physical signs are interpreted with this reservation in mind, relatively few of these patients had active lesions ascribable to syphilis. In 7 out of the 8 cases with positive spinal fluid findings, however, there were findings which were compatible with a diagnosis of general paralysis of the insane. The authors feel that this group affords evidence in favor of routine lumbar puncture on all cases with positive Wassermann reaction, for the age of malaria years earlier might have prevented their breakdown. Apart from this group there are only 7 noncertified patients with serious lesions definitely attributable to syphilis. This gives 15 patients with obvious gross lesions, or 2 percent of all noncertified cases.

Results at Tooting Bec show that infection with syphilis is by no means incompatible with the attainment of a ripe old age. One of the patients was a woman who was 100 years old and had a strongly positive Wassermann reaction. It is not possible to say why the patients successfully resisted the infection so long, but there are clearly two possible factors—the patient and the organism. A relevant observation is that the prognosis is better in untreated than in inadequately treated patients.

The noncertified patients at Tooting Bec may be accepted as a fair sample of the general population over the age of 70 years. From this it may be assumed that some 10 percent of all men over 70 have been infected with syphilis. Therefore, it follows that of the generation born

in or before 1870 many more than 10 percent must have had the disease.

Psoriasisiform lesions in secondary syphilis. M. Jeff Davis and Rudolph H. Kampmeier. *Urol. & Cutan. Rev.*, St. Louis, 45: 64-66, Jan. 1941.

Cutaneous manifestations of secondary syphilis rarely simulate psoriasis, or when they do, they usually are not generalized. A case is reported which was considered most unusual in that psoriasisiform papulosquamous lesions disposed symmetrically were present over the bony prominences of the body in the characteristic sites of predilection for psoriasis. The picture, except for the mucous membrane and genital involvement, so closely resembled psoriasis that all observers agreed on a possible coincidence of acute syphilis and psoriasis.

The patient was a white male, age 17, who came to the clinic of the Vanderbilt University Hospital because of stiff joints and a rash. His Wassermann and Kahn tests were positive. He recalled having had an ulcer at the urethral meatus about a month before the appearance of the skin lesions. No local medication was applied during treatment of this patient. Four days after injection of 0.2 gm. of arsphenamine and 0.13 gm. of bismuth salicylate, improvement in the lesions was obvious, and they had completely involuted after 3 injections of arsphenamine and bismuth.

Case of diffuse muscular gummata. M. Tottie. *Acta dermat. venereol.*, Stockholm, 22: 110-111, Feb. 1941.

The case of a 54-year-old man with diffuse gummata of the musculature of the right leg is presented. He had been treated for 1 week for a venereal disease in 1912, the nature of which was unknown. In 1924 the patient suspected reinfection and sought the advice of a physician who pronounced him well. In 1922, 5 ulcers appeared on the back of the right calf. These healed spontaneously, although slowly, leaving radiating scars. The patient had cramps in

the leg and increasing difficulty in walking. Examination showed the musculature of the entire right leg to be of board-like consistency, the foot being fixed in a position of foot drop.

The blood Wassermann and Meinicke reactions were both 3 plus positive, the spinal fluid negative.

The patient was treated with arsphenamine, iodobismutol, and potassium iodide with considerable improvement of the condition.

Congenital syphilis in identical twins with dissimilar serologic reactions. Report of a case. Eliot Wolk. *Arch. Dermat. & Syph.*, Chicago, 43: 491-497, Mar. 1941.

Twin 19-year-old Portuguese Negroes reported to the out-patient department of the Boston City Hospital on July 1, 1938, for a routine check-up. Their father, mother, and a sister had received anti-syphilitic treatment; an older brother had not been examined. One twin showed positive reactions to the Hinton and Wassermann tests and the other negative reactions on several occasions. Careful anthropometric examinations and analysis of the fingerprints and palm prints proved that the boys were identical twins. Various minor stigmas found on physical examination led to the belief that both boys had congenital syphilis. Wolk does not believe it possible that one was infected while the other was normal, and the most plausible explanation for the dissimilar serologic reactions in the twins, he says, is that a spontaneous serologic reversal took place in one of them.

Parrot's pseudoparalysis as a manifestation of congenital osseous syphilis. Thomas M. Palmer. *Urol. & Cutan. Rev.*, St. Louis, 45: 76-78, Feb. 1941.

A clinical manifestation of congenital osseous syphilis, which Palmer says is frequently encountered in the Duval County Hospital, Jacksonville, is the so-called Parrot's pseudoparalysis. This consists of inability or definite disinclination on the part of the infant to move

one or more extremities. This condition often calls to mind every diagnosis except the correct one. Rheumatism rarely seen under 3 years of age and scurvy occurs rarely earlier than the sixth month. Findlay has said that the loss of power in the limb of an infant under 6 months of age is due to syphilis.

The pathologic picture is one of osteochondritis. Clinical observation would seem to favor some mechanism other than that of the bone lesion; the speedy return of function following even a small dose of sulfarsphenamine is striking, although the X-ray showed no improvement whatsoever in the bone lesion. Unlike Pehu, Palmer has found that motion of the affected part usually causes pain.

Eight cases are briefly outlined. The infants varied in age from 5 weeks to 18 months. In each case the child would cry upon the handling of some extremity and there seemed evidence of soreness. Serial roentgenograms were made in each of the cases, and each showed manifestations of congenital osseous syphilis. These osseous lesions have eventually disappeared following continued treatment with the arsenicals. The diagnosis of Parrot's pseudoparalysis was made in each case.

Parrot's pseudoparalysis. Clinical-radiologic contribution with special reference to eye findings. A. Masia. *De mensifilografo*, Milano, 15: 737-78, Dec. 1940.

The author studied the clinical and roentgen-ray findings of 12 cases of Parrot's pseudoparalysis in infants observed by him during the past 12 years in the pediatric clinic of the University of Sassari.

According to Parrot the characteristic findings in this condition are detachment of the epiphyses from the end of the metaphyses and pain, without any necrotic findings in the nervous and muscular systems. According to other authors, however, the nervous and muscular systems may be involved. As a matter of

act the bone changes may be slight or absent and the muscular weakness marked. In one of the cases described, the symptoms of the right upper extremity and of both lower extremities were typical but no epiphyseal lesions could be demonstrated on roentgen-ray examination, the only finding being periostitis of the ends of the long bones of the lower extremities. There were no bone changes in the right upper extremity and those of the lower extremities persisted after the pseudoparalysis had disappeared, which seems to indicate that the bone changes do not explain the clinical syndrome. The author attributes the findings of the upper extremity to other factors, probably changes in the muscles or nerves.

In one case there was convergent strabismus and in another lack of convergence. The first case also had circumscribed atrophy of the iris. The fundus of the eye showed peripapillar brownish pigmentation in 3 cases, pallor of the optic disc in 1, slight neuritis and retinal edema in 5 cases, and pigmented retinal atrophy in 2 cases.

TREATMENT

chemotherapy and the early cure of gonococcal infection. O. F. Cox, Mary McDermott and W. A. Hinton. Tr. Am. Neisser. M. Soc., New York, 1940, pp. 49-52.

For this report the criterion of cure is a series of consistently negative cultures during 3 months of sustained clinical inactivity, by which is understood no purulent urethral discharge and a negative vo-glass test. A large percentage of gonococcal infections of the male genital tract eventually subside clinically and bacteriologically even without treatment, provided the body defenses are permitted to function normally. In 200 consecutive admissions to the Boston Dispensary 183 patients became clinically inactive during the period of observation, whereas the remaining 17 were still clinically active

when they left the clinic. Of the 183 patients, 70 percent became clinically inactive by the end of the 4th week, 93.5 percent by the 12th week, and 100 percent by the 36th week.

Sulfonamides have been administered at the Boston Dispensary in more than 1,100 cases; sulfanilamide in 287, disulon in 485, uleron in 237, sulfapyridine in 83, and sulfathiazole in 56. No serious reactions were noted in patients treated with sulfanilamide; disulon caused fewer minor reactions than sulfanilamide. Uleron caused no serious reactions; 2 patients given sulfapyridine developed gross hematuria.

A study of 301 case histories was made. These included only those patients who were admitted during the first week of infection and who were observed for a minimum of 3 months after they became clinically negative. Cases that were not cured within 2 weeks are reported as sulfonamide failures. Those treated with sulfathiazole were not included. Among these 301 cases, 181 remained clinically active for less than 2 weeks, but 81 of these had either a positive culture or a clinical relapse. Therefore, 100 (33 percent of the total) represents the early cures that can be definitely ascribed to the sulfonamides.

Of the series, 111 were treated with sulfanilamide, and 32 (29 percent) were cured according to the criteria. Of the 129 treated with disulon, 49 (38 percent) met the requirements of cure; of the 41 treated with uleron, 8 (20 percent); and of the 20 treated with sulfapyridine, 11 (55 percent).

Observations on the absorption, excretion and distribution of sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole. Elias Strauss, Francis C. Lowell, F. H. Laskey Taylor and Maxwell Finland. Ann. Int. Med., Lancaster, 14: 1360-1382, Feb. 1941.

Data are presented concerning the blood concentrations and urinary excretion of sulfanilamide, sulfapyridine, sulfathiazole, and sulfamethylthiazole and of the sodium salts of the latter three drugs after the administration to human

subjects of a single 5-gram dose by various routes.

In general, the sodium salts given intravenously or orally yielded higher blood levels, and these levels were attained more rapidly than when the corresponding drugs were given by mouth. The highest levels were obtained with sodium sulfathiazole.

Sulfathiazole and its sodium salt were excreted more rapidly into the urine than either sulfanilamide or sulfapyridine. All the drugs, with the exception of sulfamethylthiazole, were excreted more or less quantitatively after intravenous or subcutaneous injection, and almost all of the administered drugs were recovered from the urine after their oral administration. Only about 60 percent of administered sulfamethylthiazole was recovered from the urine, regardless of the route by which it was given.

Sulfathiazole showed the least amount of conjugation and sulfapyridine showed the most. After oral administration of sodium sulfapyridine, the percentage of acetylated drug in the blood and urine was considerably lower than that found after sulfapyridine itself was given by mouth.

Different subjects varied with respect to their absorption, excretion, and conjugation of the different drugs. There were apparently fewer variations with sulfathiazole than with any of the other compounds.

Sulfanilamide was fairly well absorbed from the rectum. All the other drugs were poorly absorbed, absorption being only slightly better when the sodium salts were used.

The para-acetyl derivatives of sulfanilamide, sulfapyridine, and sulfathiazole were poorly absorbed after oral administration. The acetylsulfanilamide was absorbed somewhat better than the others. Only a small percentage of these drugs was deacetylated in the human body.

The four compounds were found to distribute themselves differently between the blood plasma and the red blood cells. Sulfanilamide was found in the red blood

cells in greater concentrations than the plasma, sulfapyridine was about equally distributed, sulfathiazole was present in somewhat greater concentrations in the plasma, and sulfamethylthiazole was found mostly in the plasma.

Sulfathiazole was cleared from the blood at a greater rate and sulfamethylthiazole at a lower rate than either sulfanilamide or sulfapyridine.

Data are also presented concerning the concentration of sulfanilamide, sulfapyridine, and sulfathiazole in body fluids and organs of 19 patients who died during treatment with these drugs. There were considerable variations among the different cases. The concentrations of the drugs were higher in the bile and lower in the spinal fluids than in the blood. Sulfathiazole was present regularly in the spinal fluid in about one-third the concentration found in the blood. Sulfapyridine and sulfathiazole were found in the kidney in considerably higher concentrations than in the blood and other organs. The concentrations of sulfanilamide were about the same in the various organs studied, including the kidney. In the liver, the amounts of acetylated drug were always less, although the concentrations of free drug were frequently higher than in the blood. This was true of all three drugs.

Encephalopathy associated with sulfamethylthiazole therapy. Ephraim Roseman and Charles D. Aring. *New England J. Med.*, Boston, 224: 414-420, Mar. 6, 1941.

The authors report the case of a 32-year-old male Negro who died following treatment with sulfamethylthiazole for pneumonia. The dosage was 60 grains (4 gm.) every 4 hours, day and night, until the patient had been given a total of 1,680 grains (112 gm.). The treatment was discontinued when the patient complained of vertigo and vomited several times. On the evening of the day on which the treatment was discontinued, he had projectile vomiting of blood-tinged fluid, a profuse diaphoresis, and loss of vision. He then became semicomatose

the pupils were widely dilated and reacted poorly to light. Fundus examination revealed fresh hemorrhages along the border of the superior temporal retinal artery of the right eye and in the macular regions of both eyes. The next day the patient was disoriented and irrational and still had amaurosis. There was no paralysis of the extremities, the tendon reflexes were normal, and no abnormal reflexes were elicited. One hour after a lumbar puncture was performed on this day, he had a generalized convulsion, after which the right pupil was larger than the left, the right side of the mouth drooped, and the tendon reflexes on the right were hyperactive. The patient had no other generalized convulsions, lapsed into respiratory failure, and died 6 hours after the onset of convulsions. During the final 24 hours he was anuric.

Post mortem findings included discrete and confluent petechial hemorrhages scattered in the gray matter and nuclear structures. Symmetrical involvement was found wherever vertical sections of the hemispheres and brain stem included comparable halves of the nervous system. The lesions were most marked in the tail of the caudate nucleus on both sides where they measured 8 mm. in diameter, and in the mammillary bodies. Smaller diapedetic hemorrhages were noted in the substantia nigra, thalamus, and the gray matter of the convolutions. The white matter was entirely spared. The thalamus appeared to be swollen.

In the sectioned brain stem the striking feature was the bilaterally symmetrical, coalescent, diapedetic hemorrhages involving the nuclear masses of the pons and the medulla.

In the gray matter of the cerebral hemispheres (cortex and basal nuclei) and brain stem there was a moderate number of discrete perivascular foci of necrosis. The cortical architectonics in the areas containing the hemorrhagic lesions were markedly distorted. There was a notable absence of nerve cells,

with an increase in neuroglia. Many ghost neurones were present. Satellitosis and neuronophagia were marked.

The findings in this case are in contradiction to those found in typical arsphenamine hemorrhagic encephalitis, in which the white matter of the brain is the focal point of attack. However, the morbid processes found in this case and those found in the typical arsphenamine hemorrhagic encephalitis are similar in that they both demonstrate, in addition to the diapedetic hemorrhage, widespread and severe vascular disorder in the gray or white matter, with associated perivascular foci of necrosis. Why one toxin should involve the white matter and the other the gray matter is not clear and needs further investigation.

The neuronal changes present were evidently secondary to anoxia. According to the authors, two pathologic processes manifest themselves simultaneously in the hemorrhagic encephalitis induced by arsphenamine and sulfamethylthiazole, as follows: (1) The thrombotic capillary lesions lead to the focal areas of hemorrhage or perivascular necrosis, probably depending on the severity and speed of the process. (2) The varying degree of endothelial proliferation produces a disappearance of cortical ganglion cells, usually of a patchy nature.

The patient had been employed as a shaker in a lead factory for 15 years, and had probably inhaled large quantities of lead dust. There was, however, no history of colic, constipation, anemia, or nerve palsies. A high concentration of lead was found in the tissues. The authors do not believe that lead could have produced the acute pathologic and clinical symptoms of this patient. They believe that the administration of large quantities of sulfamethylthiazole, and the accumulation of the drug in the blood and tissues (due, in part, to renal failure and closely associated with acutely developing signs of severe neurologic damage) are suggestive evidence that sulfamethylthiazole was the etiologic factor involved.

Genitoinfectious lesions in the male complicated by gonorrhea. George Shrop-shear and Donald K. Hibbs. Tr. Am. Neisser. M. Soc., New York, 1940, pp. 100-104.

It is not uncommon to find gonorrhea associated with other genitoinfectious lesions in the male. During the year 1939, 306 cases of primary and secondary syphilis in male patients were diagnosed at the Chicago Municipal Social Hygiene Clinic. In 33 of these cases (10.7 percent) primary or secondary syphilis was observed in patients with gonorrhea. In 18 of these 33 patients, the syphilis developed while the patients were under treatment for gonorrhea. The primary lesion was intrameatal in 30.3 percent of these cases. Not infrequently chancres involving the prepuce may give rise to a phimotic edema which may be confused with the inflammatory phimosis associated with severe cases of gonorrhea.

To every patient with gonorrhea and infectious early syphilis, sulfanilamide in the usual dosage and nearsphenamine intravenously at intervals of 3 to 4 days were administered. In no instance was there any severe toxic manifestation.

Among 73 cases of chancroidal infection in the male there were 3 patients with a complicating gonorrheal urethritis. When this complication occurs, treatment is greatly simplified by the fact that both diseases respond favorably to the oral administration of sulfanilamide. In 105 cases of venereal lymphogranuloma there were 4 patients in whom mixed infection with gonorrhea occurred. The therapeutic dose of sulfanilamide in gonorrhea is equally satisfactory for the associated venereal lymphogranuloma. Three out of 7 cases of granuloma inguinale in the male were complicated by gonorrhea. Concurrent intramuscular injections of fuadin and sulfanilamide in such cases have given no untoward results.

Gonorrheal vulvovaginitis in children.

Michael Levin and David S. Koransky. Urol. & Cutan. Rev., St. Louis, 45: 10-107, Feb. 1941.

Recent advances in knowledge of chemotherapy and the estrogens has made possible to treat gonorrheal vulvovaginitis in children with success. In 18 cases treated in the children's division of the Cook County Hospital (1938-1940) cure was effected in 150 or 94.93 percent. From a study of these cases, the authors reach the following conclusions:

The continued observation of local findings in gonorrheal vulvovaginitis by vaginoscopic examination is of equal importance with bacteriologic study. There appears to be a definite relationship between the protective mechanism of estrogenic reaction in the neonatal period and the development of gonorrheal vaginitis. Adequacy or artificially induced estrogenic reaction bears a direct relationship to the acidity attained. There is no relationship between the duration of infection and facility with which cure can be established.

In this series of 158 patients, 18 (11.4 percent) presented abdominal (14) or arthritic (4) complications on admission. Among 100 children the complement fixation test was of no value in establishing a diagnosis in uncomplicated cases. It was positive in 4 out of 6 children with complications.

Before determining the final diagnosis of cure a period of 6 months of observation with vaginoscopic and bacteriologic study is advisable.

Sulfanilamide therapy was successfully employed in 72 (59.5 percent) of 121 children. When gonorrheal patients respond to sulfanilamide, success is dramatically attained within 2 weeks. Blood chemistry studies demonstrate that failures apparently did not result because of lack of adequate free sulfanilamide blood concentrations. Approximately 10 percent of sulfanilamide

ected patients developed reactions sufficiently severe to interrupt treatment.

In a series of 70 children treated with trogenic suppositories success was attained in 55 (78.57 percent), approximately one-half of which were within 2 weeks, closely coinciding with the appearance of a pH of 4.5 to 5.5 and attained by a dose of from 7,000 to 20,000 U.

Among 21 patients treated with sulfaridine there were 17 successes (80.95 percent). These patients had the shortest period of hospitalization. The incidence of toxic reactions was high among these patients.

Diathermy and protargol instillations were of use.

Influence of vitamin C therapy on arsenical sensitivity. A. Denton Vail. J. Missouri M. A., St. Louis, 38: 110-120, Apr. 1941.

A preliminary report on the study of the influence of vitamin C on arsenical sensitivity is given. A review of the literature to date is presented.

Of 300 clinic patients treated with arsenicals for syphilis, 48 percent had complaints referable to arsenical medication. Of these, 98 percent were women and 2 percent were men. Not all of these patients proved to be actually sensitive to arsenicals. Some of the complaints may have had a psychic basis. No examination was offered for the preponderance of women complainers.

A control group of 10 patients was selected. These patients had had at least 10 injections of neoarsphenamine without reaction of any kind. Weekly vitamin C determinations were made on all these patients just prior to treatment over a period of 6 to 9 weeks. There was no significant difference in the vitamin C determinations of males and those of females. All had values well within normal limits. A correlation of therapy with blood vitamin C levels showed that the type of antisyphilitic treatment had no effect upon the vitamin C values.

A group of 15 patients who complained of reactions to neoarsphenamine in vary-

ing degrees was next selected for study. Patients complaining of relatively minor symptoms were given vitamin C by mouth, those complaining of more severe manifestations were given intravenous medication, while those complaining of still more severe reactions were given vitamin C by mouth and intravenously. Oral medication consisted of tablets of ascorbic acid (Cebione) in doses of 50 to 100 mg. daily. Intravenous medication consisted of the inclusion of 100 mg. of crystalline ascorbic acid in each 10 cc. of solution containing 0.6 gm. neoarsphenamine (1 percent solution of vitamin C).

Weekly blood vitamin C determinations were made on these patients for several weeks prior to the institution of vitamin C therapy in order to arrive at a more accurate estimate of the constant value for a particular patient. Patients taking vitamin C by mouth were given this drug 1 week prior to the administration of the arsenical. During the administration of bismuth courses no vitamin C was given. Detailed data is tabulated for each of the 15 patients.

The author's conclusions are as follows:

1. Arsenical sensitivity is most commonly associated with hypovitaminosis C.

2. Arsenical reactions occur in the presence of normal blood vitamin C values in a small percentage of cases. These warrant investigation to rule out psychic and other factors.

3. Oral administration of the vitamin is effective but slower and subject to variations within the organism. Best results will be obtained in the majority of patients by intravenous methods. Severe cases may respond only to combined oral and intravenous therapy.

4. Spectacular relief from symptoms of arsenical sensitivity may be obtained by the use of relatively small doses of vitamin C given in conjunction with arsenical medication.

5. Progressive increase in blood vitamin C values is obtained through the administration of vitamin C in doses heretofore thought to be too small to be effective.

6. Inclusion of vitamin C in arsenical therapy does not lessen the therapeutic response to the arsenical.

7. In general, as blood vitamin C values improve, symptoms of arsenical sensitivity disappear. Recurrence of symptoms is usually reflected in a lowering of the blood values.

8. Vitamin C is a valuable adjunct to antisyphilitic therapy.

The author emphasizes the need of continued and more extensive investigation of this subject.

Practical considerations in the treatment of congenital syphilis. Belle Korman, Mary D. Smith and Arthur F. Abt. *Urol. & Cutan. Rev.*, St. Louis, 45: 121-126, Feb. 1941.

At the Municipal Social Hygiene Clinic, Chicago, the infants whose mothers' treatment for syphilis began in the last half of pregnancy are followed up by making an X-ray film of the long bones upon the first visit to the clinic, and a monthly serologic and physical examination until the age of 6 months, at 1 year and yearly thereafter until puberty, if possible.

Acetarsone given orally is used in treatment of infants less than 1 year old and for a few older children who attend the clinic regularly and whose mothers are reliable and intelligent. The dosage used, per kilogram of body weight, is 0.005 gm. of acetarsone daily for 1 week, 0.01 gm. for 2nd week, 0.015 gm. for 3d week, and 0.02 gm. for 4th through 9th weeks. From the 10th through the 15th week, bismuth salicylate; 16th week, acetarsone 0.01 gm. per kilogram daily; 17th through 24th week, 0.02 gm.; 25th through 30th weeks, bismuth salicylate. The dosage of bismuth salicylate is: 6 months of age, $\frac{1}{8}$ cc.; 6 mos. to 1 yr., $\frac{1}{4}$ cc.; 1 yr. to 4 yrs., $\frac{1}{2}$ cc.; 4 to 8 yrs., $\frac{3}{4}$ cc.; 8 to 12 yrs., 1 cc.; 12 yrs., $1\frac{1}{2}$ cc.

During the past 4 years 98 infants and children were treated with acetarsone at this clinic, 70 children being under 1 year of age. There were 28 who received 3 or more courses and 31 had only 1 course.

Serologic reversal occurred in 25 after the first course, in 15 after the second course and in 3 after the third course of stovarsol and bismuth, a total of 43 percent. Only 1 week's supply of the drug is usually given to the mother. In only 4 cases was the medication changed. The use of acetarsone did not result in better attendance, however.

Thirteen children had mild gastrointestinal complaints, usually a slight diarrhea; 5 had questionable exanthemata. In 4 cases the drug had to be permanently discontinued—in 1 case because of severe diarrhea (a rash developed in this case when it was attempted to give the drug again after a rest period), in 3 cases because of a rash, and in the fourth case because of albumin, casts, and erythrocytes in the urine. Transient albuminuria occurred in a few others.

In the treatment of early asymptomatic congenital syphilis the intensive continuous routine of the early congenital is usually advised, while in the late asymptomatic type rest periods are permissible. In this clinic, however, the continuous method is used throughout for at least 4 years. Courses of 12 injections of neoarsphenamine and from 12 to 16 injections of bismuth are given until at least 40 to 50 injections of an arsenical and 50 to 60 injections of bismuth have been received. In interstitial keratitis routine intensive treatment is given in maximum doses suitable to age and weight until the attack subsides.

The importance of the nutritional state of the growing child in his response to treatment is well recognized.

The South Side branch clinic of the Municipal Social Hygiene Clinic has grown rapidly. From July 1, 1939 to June 30, 1940, 22,733 visits for examination and medical care were made by congenital syphilitic children and mothers. In addition 1,832 children (familial contacts), were examined, 158 of whom were found to have positive serology. The psychologic effect of treating both mother and child in the same clinic is excellent.

Intensive treatment of early syphilis.
Herbert Rattner. Illinois Health Messenger, Springfield, 13: 44-47, Mar. 1, 1941.

As one of a group of 5 medical centers organized in the Middle West to undertake a cooperative group study of the day intensive method of treatment of early syphilis, a treatment station was started in August 1940 at the Cook County Hospital. Since then 65 patients have been treated. Only those patients are selected who have early syphilis, with primary or secondary manifestations definitely diagnosed. The prospective patients are told that the treatment is still in the investigative stage and that it is not without some danger. Before treatment each patient undergoes a thorough physical examination, with considerable laboratory work. Before discharge the venereal index is determined and the spinal fluid examined. No patient is discharged sooner than 2 full days after treatment has been completed, and he is told to report to the clinic for examination weekly for 4 weeks and then monthly.

At the Cook County Hospital at present arsphenamine is being used, in the amount 0.24 gm. dissolved in 2,000 cc. of 5 percent glucose solution in triple distilled water for a day's supply. Through a short 20-gauge needle the solution flows to a vein at the rate of 40 to 50 drops per minute. A different vein is selected each day.

Of 65 patients treated since August 1, 33 were men and 21 women. There were 17 white men, 6 white women, 29 Negro men, and 15 Negro women. Of these, 23 had primary syphilis, and 42 had secondary manifestations. Their ages ranged from 17 to 51 years.

There have been a number of minor reactions and side effects, and a few that were serious. Fever, nausea and vomiting, and pain in the arm occurred in most all of the patients. Cerebral complications occurred in 2 patients, 1 of

whom suffered a genuine toxic encephalitis which occurred after completion of treatment. He was in excellent condition when discharged from the hospital after about 2 months. His Kahn reaction was negative after 6 weeks and was still so a month later. In the other case with cerebral complication, treatment was discontinued after the third day, and this was the only case which received less than the full 5 days' treatment. Toxidermas were seen but twice in the series. Herxheimer reactions, with accentuation of the cutaneous lesions, occurred in 5 cases. So far there have been no instances of exfoliative dermatitis, or of renal, hepatic or other parenchymal damage, and no cases of hemopoietic or nitritoid reactions.

Experience with the 5-day treatment method has been too recent to give final clinical evaluations. Spirochetes disappeared from lesions in a day or two, and all open lesions have healed during the period of hospitalization. Spinal punctures, which were performed on each case, have shown normal spinal fluid. Of the first 40 patients 11 failed to return for follow-up studies. Of those who returned, 10 who had strongly positive serologic reactions before treatment had negative reactions 8 to 10 weeks later; 4 others with strongly positive reactions before treatment had doubtful reactions after 10 weeks; all others had a marked reduction in the quantitative titers as determined by the Kahn test. Apparently reversal of the serologic reactions occurs earlier in those cases which are treated earlier. In the few cases where it was necessary for some reason to interrupt treatment temporarily there was for a time a sharp rise in the quantitative titer but otherwise no untoward developments.

While this method appears to be promising it is not yet ready for general use. Only 15 cases have been followed for a 5-year period, and no observations are available as to the final outcome so far as cardiovascular syphilis or neurosyphilis are concerned.

PATHOLOGY

Encephalopathy following neoarsphenamine therapy. Ephraim Roseman and Charles D. Aring. *New England J. Med.*, Boston, 224: 550-553, Mar. 27, 1941.

The authors briefly review the literature on this subject. They report the case of a 27-year-old Negro woman who died from encephalopathy following the fifteenth injection of neoarsphenamine.

Antisymphilitic therapy had been given in this case because serologic tests had been positive on two occasions (April 25 and June 1, 1940). During the period from June 19, 1939 to February 23, 1940, two courses of bismuth subsalicylate in oil (2 cc. per dose) and two courses of neoarsphenamine (0.6 gm. per dose) were given. By February 23, the patient had been given the fifteenth dose of neoarsphenamine.

On February 25, the patient had a headache and felt dizzy. On February 27, she became delirious and lapsed into coma. On this day, her pupils measured 6 mm. in diameter. They dilated widely to bright light and slowly contracted through only a small range despite the maintained light. The eyes tended to wander to the left but were quickly jerked back to the midline with coarse, nystagmoid movements. The optic fundi were normal. There was, at times, increased resistance to passive movements of all the muscles of the trunk and extremities. These periods were marked by tonic extensor spasm, which lasted from 15 to 20 seconds. Following these episodes, muscular tone became notably decreased, and the respirations became slow and shallow. There was no spontaneous, purposeful movement. The tendon reflexes in the arms and legs were hyperactive bilaterally. The Hoffmann sign was strongly positive on both sides, and the plantar responses were flexor bilaterally. No abdominal reflexes were obtained. There

was mild stiffness of the neck, but Kernig or Brudzinski signs were elicited. A lumbar puncture performed at this time revealed an initial pressure of 3 mm. of water. The cerebrospinal fluid was clear and colorless and contained lymphocyte and 3 red blood cells per cubic millimeter. The Pandy reaction was three plus, and the total protein was 2 mg. per 100 cc. The cerebrospinal fluid Wassermann reaction and gold-sol curves were negative.

By the next day (February 28) the tonic extensor spasm had disappeared. Muscular resistance and tendon reflexes were normal and equal in all extremities. A second lumbar puncture at this time revealed a cerebrospinal fluid pressure of 200 mm. T fluid was clear and colorless. It contained no white cells but 8 red cells. T Pandy reaction was one plus. The patient died on February 29.

Post mortem findings included, in addition to pathologic changes in the nervous system, confluent lobular pneumonia with acute fibrinous pleuritis, acute bronchitis, left ventricular hypertrophy, severe toxic hepatosis and focal necrosis of the liver, acute splenitis, toxic nephrosis, early atherosclerosis of the aorta, mild pleural fibrosis, cystic right ovary, intracanalicular fibroadenoma of the breast, a leiomyoma of the uterus.

The convolutions of the brain were moderately flattened and broadened, and the vessels of the meninges were congested. There was herniation of the uncus of the temporal lobe on both sides, more marked on the left. There was well-defined cerebellar pressure contusion, which, although small, was sharply indented, particularly on the left side.

Throughout the white matter of the sectioned brain there were discrete confluent bright red, pin-point lesions, resembling petechiae, which tended to involve both hemispheres symmetrically. The authors do not think these were important factors in the analysis of the lesions.

According to the authors, the most important lesions found in the nervous system

n were widespread and multiple foci perivascular softening and demyelination which were disseminated throughout the cerebral hemispheres but which were absent in the brain stem. This perivascular necrosis was not related to the hemorrhage and was present only in the white matter. In the centers of such lesions capillaries or precapillaries with markedly swollen or completely destroyed endothelium could be seen. Immediately surrounding each central vessel was an area of necrosis which was relatively acellular but in which a few macrophages with ingested pigment were noted.

The changes in the nerve cells of the hemispheres and brain stem were widespread and consisted chiefly of moderate to severe chromatolysis. There was some cellular proliferation. No histologic evidence of syphilis was seen.

There were no signs of pneumonia before the patient died, although evidence of the disease was found at autopsy. The clinical signs were those of an overwhelming neurologic catastrophe that resulted in death 88 hours after the initial symptom of a slight headache. However, the possibility that an acute infection was responsible for the encephalopathy cannot be discarded.

LABORATORY RESEARCH

The toxicity and trypanocidal activity of commercial neoarsphenamine. C. A. Morrell and M. G. Allmark. J. Am. Pharm. Assoc., Scient. Ed., Washington, 30: 33-38, Feb. 1941.

The toxicity of neoarsphenamine, arsphenamine, and sulfarsphenamine sold in Canada is subject to regulations under the Food and Drugs Act of Canada. The toxicity is expressed as a percent of the International Standard preparation. Batches of the drugs having toxicities

greater than 120 percent are not sold in Canada.

The authors report the results of approximately 200 routine assays of neoarsphenamine for toxicity and 76 tests for trypanocidal activity. It has previously been recommended that the trypanocidal activity of commercial neoarsphenamine should not be less than 80 percent of the International Standard.

The materials and methods used are described in detail.

The toxicities of the products of nine different manufacturers averaged from 80 to 115 percent of the International Standard. There was no doubt that some neoarsphenamines were better than others (judged by these tests). Three of the brands were definitely superior because their toxicities were low and they had little variation from lot to lot.

Neoarsphenamine having a low toxicity need not have a low trypanocidal activity. Most of the brands tested which showed a low toxicity had a high trypanocidal potency. The most toxic were usually, though not always, the least active. One manufacturer prepared a product with uniformly low toxicity which was at the same time the most potent of those examined.

Single-dose and multiple-dose variations of the methods for toxicity and trypanocidal activity were used in this study. The simplicity of the one-dose technique, especially in the calculation of results, is a strong recommendation in its favor, especially in routine assays where a large number of tests must be done each week. However, it is not advisable to adopt this method until experience gained with the animals and drugs used has indicated that it is feasible. It should not be employed when investigating new substances or in research problems.

Steeper dosage-response curves yield more accurate assays. They imply less individual variation in the test animals. Every effort consistent with economy of labor and material should be made to increase their slopes. Individual variation may be reduced by maintaining a

satisfactory and constant environment and by close inbreeding of the animals.

The authors were unable to increase uniformity significantly by inbreeding their test animals. Other investigators, however, have shown definitely that considerable improvement in accuracy results from the use of a carefully bred and tended stock of animals.

The slopes of the regression lines for sulfarsphenamine, arsphenamine, and mapharsen were computed for a few assays, using male rats in most of the tests. The numerical results are reported.

The following tables are presented: (1) Toxicity of 4 Canadian standards for neoarsphenamine in terms of the International Standard. (2) Trypanocidal activity of 2 Canadian standards for neoarsphenamine in terms of the International Standard. (3) Toxicity of 9 brands of neoarsphenamine offered for sale in Canada. (4) Trypanocidal activity of 4 brands of neoarsphenamine offered for sale in Canada. (5) Ratio of trypanocidal activity to toxicity of some brands of neoarsphenamine sold in Canada. (6) Slope of the regression lines which show dosage-mortality relationship for the determination of the toxicity of neoarsphenamine using albino rats. (7) Difference in the slope of the regression lines for the toxicity of neoarsphenamine due to the sex of the rats. (8) Slope of regression lines showing dosage-response relationship in the determination of the trypanocidal value of neoarsphenamine using albino rats.

Cyanosis in treatment with sulfonamide compounds. N. Svartz and S. Kallner. *Acta med. Scandinav.*, Stockholm, 104: 309-312, 1940.

These authors point out that the cyanotic discoloration of the skin in patients treated with sulfonamide compounds is due to a darkening of the blood which is associated with the erythrocytes and not due to the presence of either methemoglobin or sulfhemoglobin. A study of the oxygen-combining power of the blood showed that the cyanosis in these cases was not of the ordinary type. It was

found that when erythrocytes from patients treated with sulfonamides washed with physiologic salt solution and then shaken with air, they assume a light color of normal blood, whereas washed erythrocytes either do not become lighter in color or only very slightly. The substance responsible for the darkening of color easily diffuses through the membrane of the erythrocyte into the plasma. This can be demonstrated by adding plasma from patients treated with sulfonamides to normal erythrocytes. The latter will be found to become darker in color and will retain this dark coloration even when shaken with air. The authors therefore assume that the darkening of the blood is due to the fact that a substance, colorless in itself, and present in both erythrocytes and plasma, forms a colored combination with some constituent normally occurring in the erythrocytes. By dialysis of blood obtained from a person treated with sulfonamide the substance causing the darkening of the erythrocytes can be obtained in solution and afterwards concentrated. The addition of even a very small quantity of concentrated dialysate is enough to prevent normal erythrocytes from becoming lighter in color when shaken with air. But if the blood is first shaken until it assumes a lighter color it will not become dark on the addition of the dialysate. Reduced hemoglobin is therefore necessary to bring about the darkening of the blood. Further experiments, which are to be reported in detail later, showed that in all probability the cause of the darkening of the blood and of the cyanotic discoloration of the skin are the amide constituent of the sulfonamide compounds and the porphyrin group in the hemoglobin. These investigations are being continued.

Studies on the supposed incompatibility of arsphenamine and sulfonamides. Caletti. *Dermosifilografo*, Milano, 707-712, Nov. 1940.

Streptosil (para-amino-phenyl-sulfonamide) in a dosage of 0.2 gm. per kg. a neoarsphenamine in a dosage of 0.2

3 gm. per kg. were simultaneously administered to a series of 10 rabbits and guinea pigs.

1. Streptosil was injected intramuscularly in an amount of 10 cc. of a 2-percent solution per kg.; neoarsphenamine was also injected intramuscularly in doses of 10, 0.2, and 0.3 gm. per kg. Treatment was given every 3 days for a period of 10 days. No noticeable effects of this treatment were observed.

2. Intravenous injection of neoarsphenamine, in a dosage beginning with 0.08 gm. per kg. and increasing in a month up to 0.30 gm. per kg. was immediately followed by intravenous injection of 10 cc. of 2 percent streptosil per kg., injections being given at 3-day intervals. The animals remained normal in every way and gained weight.

3. Injections were made as in 2, except that the neoarsphenamine solution was added to the streptosil solution before being injected. No untoward effects were observed.

When the dose of neoarsphenamine contained in the streptosil solution was increased up to 0.60 gm. per kg., rabbits died 30 hours after injection of this dose.

Over a period of 6 months, 15 persons received simultaneous treatment with streptosil and neoarsphenamine because they had both syphilitic and gonorrheal infections, without ill effect.

These findings indicate that treatment with arsphenamines and sulfonamides may be safely given at the same time.

Intravenous toxicity of heparin-sodium sulfapyridine combinations and protective action of barbiturates. N. A. David, N. M. Phatak, H. Donnell and H. Vehrs. J. Am. Pharm. Assoc., Scient. Ed., Washington, 30: 38-40, Feb. 1941.

In cases of subacute bacterial endocarditis it would seem desirable to give a chemotherapeutic agent simultaneously with the intravenous administration of heparin in order to clear the blood stream of the invading microorganisms and at the same time to prevent further depositions of thrombotic masses on the heart

valves. The authors report the results of experiments on 7 dogs to determine the safety of such treatment. Five of the dogs survived the experiments.

The most constant side effects noticed after the oral or intravenous administration of toxic doses of sodium sulfapyridine to the dogs were nausea, vomiting, generalized clonic and tonic convulsions, acidosis, drug fever, coma, and finally death. Moderate or even therapeutic amounts caused nausea, salivation, vomiting and often mild jerky muscular tremors. Since the mixtures were administered intravenously, the toxic effects noted must be attributed to central nervous system stimulation rather than to local gastric irritation or to a reflex therefrom. In all animals repeated administrations of ether inhalation or a single parenteral injection of 15 to 20 mg. per kg. of sodium pentobarbital was sufficient to prevent the convulsive seizures and to prevent the muscular exhaustion of the animals. However, ether administration alone failed to protect the animals completely. Intraperitoneal injection of 15 to 20 mg. per kg. of sodium pentobarbital given 20 to 30 minutes previous to or soon after completion of the injection of sodium sulfapyridine not only minimized the toxicity of the drug but completely protected the animals from convulsive seizures and certain death. When sodium pentobarbital was given in conjunction with the intravenous administration of sodium sulfapyridine and heparin mixtures, the dogs invariably recovered completely from the effects of the drugs in less than 24 hours. This use of the barbiturate (a short-acting one) was not only spectacular but a definite life-saving measure. It should be therapeutically valuable in counteracting the toxic effects of sulfonamides administered to humans.

A mixture of sodium sulfapyridine and heparin remains stable in solution for at least 6 to 10 hours and often as long as a week (dependent on the condition of storage). Such a mixture is not stable in either a glucose or a glucose-saline vehicle.

From the results of these experiments, the authors conclude that heparin and sodium sulfapyridine mixtures may be safely administered intravenously as a continuous drip. They found that the use of sodium pentobarbital, orally or parenterally in hypnotic doses, either previous to treatment or simultaneously with it, is not only beneficial but advisable as an adjunct to reduce the untoward manifestations of sodium sulfapyridine therapy. Use of molar sodium lactate to counteract the acidosis was found preferable to either physiologic saline or glucose solutions as a vehicle for the parenteral administration of heparin and sodium sulfapyridine.

Penetration of sulfathiazole in the eye.

John G. Bellows and Hermann Chinn.
Arch. Ophth., Chicago, 25: 294-298,
Feb. 1941.

The concentration of sulfathiazole in the blood and spinal fluid and in the various ocular tissues and fluids of the dog was determined 1, 2, 4, 6, and 24 hours after oral administration of the drug. The maximum concentration was reached from 4 to 6 hours after administration of the drug. Higher concentrations were found consistently when sulfathiazole was given dissolved in hydrochloric acid than when it was given in an aqueous suspension.

In one series, the dosage given was 0.2 gm. of sulfathiazole per kg. of body weight, suspended in 15 to 20 cc. of water and administered by stomach tube to dogs under sodium pentobarbital anesthesia. Since preliminary tests indicated that the highest concentration was reached after 4 to 6 hours, the eyes were removed at these times and the constituent tissues analyzed. A similar procedure was adopted with another series of dogs, but the sulfathiazole was dissolved in hydrochloric acid before administration.

The concentrations found 4 hours after administration of sulfathiazole dissolved in hydrochloric acid were as follows: In blood, 7.4 mg. percent; aqueous humor, 0.4 mg. percent; cerebrospinal fluid, 1.0

mg. percent; lens, 0.0 mg. percent; cornea, 2.0 mg. percent; sclera, 10.4 mg. percent; chorioretinal layer, 4.9 mg. percent; vitreous humor, 0.9 mg. percent; conjunctiva, 8.4 mg. percent.

The concentrations found 6 hours after the administration of sulfathiazole suspended in water were as follows: In blood, 2.0 mg. percent; aqueous humor, 0. mg. percent; cerebrospinal fluid, 0.1 mg. percent; lens, 0.0 mg. percent; cornea, 0. mg. percent; sclera, 2.5 mg. percent; chorioretinal layer, 2.4 mg. percent; vitreous humor, 0.4 mg. percent; conjunctiva, 2. mg. percent.

The most significant finding in each group was the failure of sulfathiazole to penetrate into the aqueous humor, vitreous humor, or spinal fluid in appreciable quantities. In practically every case, less than 0.5 mg. per hundred cc. could be detected in these fluids, and in most cases less than 0.1 mg. percent.

The lens, which is nourished by the surrounding media, contained no sulfathiazole at any time. The cornea showed small amounts, with the more vascular uveal, retinal, and conjunctival tissue containing a somewhat higher concentration. The scleral tissue uniformly had the highest concentration of the drug, sometimes exceeding even the concentrations in the blood (the reason for this is unknown).

Concentrations of sulfanilamide found in dogs 4 hours after oral administration of 0.2 gm. per kg. of body weight were as follows: Blood, 18.0 mg. percent; aqueous humor, 10.9 mg. percent; vitreous humor, 8.4 mg. percent; cornea and sclera combined, 13.4 mg. percent; chorioretinal tissue, 15.2 mg. percent; and lens 2.7 mg. percent.

The concentrations of sulfapyridine found 4 hours following oral administration of the same dosage of this drug were as follows: Blood, 6.1 mg. percent; aqueous humor, 4.9 mg. percent; vitreous humor, 5.8 mg. percent; spinal fluid, 3.4 mg. percent; cornea, 6.8 mg. percent; sclera, 7.0 mg. percent; chorioretinal tissue, 6.3 mg. percent; and lens, 1.1 mg. percent.

The clinical value of sulfathiazole may be enhanced when it is given with hydrochloric acid to ensure more rapid absorption. This precaution should be of particular importance when the drug must be given to achlorhydric patients.

The value of sulfathiazole in ocular infections is decidedly limited because only traces of the drug will enter the vascular tissues and fluids of the eye. This suggests that sulfathiazole would be ineffective in endogenous and exogenous infections of the ocular media. However, justification exists for its use in gonococcal and certain other infections of the uveal, retinal, and conjunctival tissues.

Observations on the toxicology of sulfathiazole and some related compounds. H. A. Walker and H. B. van Dyke. *J. Pharmacol. & Exper. Therap.*, Baltimore, 71: 138-150, Feb. 1941.

From experiments carried out by the authors it was determined that the doses of the sodium salts of sulfanilamide, sulfapyridine, sulfathiazole, and certain analogues of sulfathiazole which, after a single subcutaneous injection into albino Swiss mice cause a mortality of 50 percent, were, in terms of millimols per kilogram body weight, as follows: Sulfanilamide, 13.45; sulfapyridine, 3.24; sulfathiazole, 5.18; sulfamethylthiazole, 3.29; sulfamethylthiazole, 0.80; sulfaphenylthiazole, 1.39.

The toxic effects of repeated doses of sulfapyridine, sulfathiazole, and sulfamethylthiazole were compared by feeding each drug mixed with food in concentrations of 0.5 and 1.0 percent to groups of growing male and female rats for 50 days. Concretions and associated damage to the kidneys, an increase in the percentage of neutrophils in the blood, as well as interference with growth, were all most strikingly present as a result of the administration of sulfamethylthiazole. Only sulfamethylthiazole caused lymphoid atrophy of the spleen in rats. Sulfathiazole caused no change in the distribution of leukocytes. In some mammals,

such as the mouse and rabbit, toxic symptoms and accompanying pathologic changes were more pronounced after oral administration of repeated doses of sulfathiazole than after sulfapyridine similarly administered.

Additional metabolic experiments in rats indicated that after administration by stomach tube, sulfathiazole and sulfapyridine were equally well absorbed during the 24 hours following a single dose, but that much less of the sulfathiazole underwent conjugation. It is probable that free sulfathiazole is removed from the blood more rapidly than free sulfamethylthiazole or free sulfapyridine whereas the conjugated drug is probably excreted differently.

Ocular lymphogranuloma venereum.

John P. Macnie. *Arch. Ophth.*, Chicago, 25: 255-279, Feb. 1941.

The author reviews the literature on venereal lymphogranuloma and on the ocular manifestations of the disease. He discusses the stages of the disease, the constitutional symptoms, various names applied to the disease, distribution of the disease, etiology, properties of the virus, immunology, transmission to animals, pathology, differential diagnosis, and treatment.

Cases of venereal lymphogranuloma have been reported showing conjunctivitis, retinal hemorrhages, episcleritis and peripapillary edema, as well as dilatation, tortuosity, or dark coloration of the retinal vessels.

Nine cases of Parinaud's oculoglandular syndrome in patients infected with the virus of venereal lymphogranuloma have been reported. In four of these the conjunctival secretion or excised conjunctival tissue has been shown to contain the virus.

A series of 30 patients with keratoconjunctivitis and uveitis were subjected to the Frei test. Of these, 4 had positive reactions and were found to have rectal symptoms consistent with venereal lymphogranuloma. Other pathologic conditions in all 4 could have accounted for the ocular symptoms, but venereal

lymphogranuloma was a possible etiologic factor in 3 of the cases.

Successful inoculations of animal eyes with the virus of venereal lymphogranuloma and successful transfer from eye to eye by means of infected aqueous humor have been reported. Infected aqueous humor has also produced characteristic meningoencephalitis in white mice, and antigens from these infected brains have given positive Frei reactions. Granulocorpuscles have been reported in scrapings from the posterior surface of the cornea of experimentally infected eyes.

An experimental study with animals was undertaken in an effort to confirm the foregoing findings. The virus used was isolated from human glandular material in August 1938. During the course of this study the virus was maintained in tissue cultures consisting of embryonic guinea pig in serum ultrafiltrate and by intracerebral mouse inoculation. The author reports the following findings: (1) Keratitis and uveitis were produced in the eyes of 13 of 19 guinea pigs by injecting infected mouse brain antigen into the anterior chamber. (2) The infection could not be introduced into other guinea pig eyes by transfer of aqueous humor. (3) Some of the same aqueous humor inoculated intracerebrally produced the symptoms of venereal lymphogranuloma in white mice. (4) Infected aqueous humor was introduced into a tissue culture, and an antigen from this culture produced a positive Frei reaction. (5) Tests for cutaneous sensitivity in 9 infected guinea pigs yielded 4 positive, 2 doubtful, and 3 negative results. (6) Smears from the iris and posterior surface of the cornea of infected guinea pig eyes, when stained according to the Giemsa method, showed structures of varying size resembling the elementary and initial bodies of trachoma.

The author says that there is no thoroughly satisfactory treatment for venereal lymphogranuloma. Reports have appeared in the literature of the use of antimony, gold, copper, and iron compounds; of salicylic acid and potassium tartrate;

of foreign protein, heat, and ultraviolet radiation; of surgical incision and excision of glands, and of dilatation or colostomy for stricture. Sulfanilamide and its related compounds seem to be valuable in this disease.

Propagation of the virus of lymphogranuloma venereum on the chorioallantois of the developing egg. Marie E. Howard and Winifred S. Hull. *Infect. Dis.*, Chicago, 68: 73-78, Jan. Feb., 1941.

The authors report a series of attempts to cultivate the virus of venereal lymphogranuloma on the chorioallantoic membrane of the developing egg. It was hoped that a simple and suitable method for titrating the virus might thus become available and that lesions might result which would serve to distinguish the virus from others producing a round cell meningo-encephalitis following the intracerebral inoculation of mice. The materials and methods used are described in detail.

Seven separate attempts were made to propagate the virus. In four the virus was successfully carried for 6, 8, 10, and 12 generations, respectively, before the work was stopped. In three instances the virus was lost by the fourth or fifth egg passage. In all of the series there was a diminution in the virulence of the virus for mice following the first egg passage.

The time at which transfers were made seemed to be an important factor in determining whether or not the virus would survive. It was found that routine passage in eggs every 2 to 4 days was more satisfactory than if a longer time between transfers was allowed to elapse.

This timing happened to be approximately the same as that used in the routine animal transfers of these strains. Infected egg membranes incubated for 2 to 4 days, often without macroscopic lesions, seemed to have a higher infectivity than those incubated for longer periods of time. Lesions were more likely to be found 4 to 6 days after inoculation than at earlier periods.

Infectivity in eggs and the antigenic tendency of infected membranes (as measured by skin tests in human cases) did not run a parallel course. Membranes with demonstrable infectivity for other eggs and membranes and for mice usually elicited only small skin reactions when made into Frei antigen, and sometimes none at all. The membranes showing minute lesions gave larger Frei tests but the evidence of infectivity.

This has its analogy in human as well as animal material. Active virus is more easily obtained from recently infected animals in which the clinical evidences of suppuration are slight. Frei antigen prepared from such glandular material usually produces only small skin reactions. The pus of old suppurating lesions has a low infectivity for animals although it makes excellent antigen.

Among the 7 series discussed by the authors, lesions were found in less than 30 percent of all membranes examined. These lesions were not distinguishable microscopically from those produced by other viruses, and it was sometimes doubtful whether they were more than the non-specific lesions which have been described in membranes of eggs which had been cleaned and incubated for 12 to 16 days. Microscopically, however, they resembled the small abscesses found in infected human glands. The low incidence of lesions made it seem that this method of propagating the virus would not provide a simple method for titrating it.

The variations in the size of the Frei tests resulting from the use of infected egg-membrane antigen indicate that the infected chorioallantois is not a reliable source of Frei antigen.

Complement-fixation test in lymphogranuloma venereum. Geoffrey Rake, Morris F. Shaffer, Clara M. McKee and Helen P. Jones. *Proc. Soc. Am. Bact., J. Bact.*, Baltimore, 41: 55, Jan. 1941.

By employing antigens derived from the yolk-sac of the developing chick embryo or the lungs of mice following in-

fection of these tissues with the agent of venereal lymphogranuloma, successful complement fixation tests have been obtained in the presence of serum from individuals with this disease. The successful demonstration of the reaction appears to depend on the fact that the antigens now used have a content of virus many thousands times as great as those previously available. The complement fixation test appears to be specific.

In 57 individuals thought to be clinically lymphogranulomatous, the serums of all fixed complement. In 28 individuals thought not to be lymphogranulomatous, the serums of 26 failed to fix complement while those of 2 did. Explanations for the reactions in these 2 cases were possible. Serums from 69 syphilitic individuals have been tested. Positive complement fixation tests were obtained in over 50 percent of them. In 23 of this group, the results of the complement fixation test were checked with Frei tests using Lygranum (yolk-sac antigen); in 17 there was complete correlation. These results suggest that there exists an extensive reservoir of latent infection with the virus of venereal lymphogranuloma in individuals who have been exposed to venereal disease.

Soluble antigen in lymphogranuloma venereum. Geoffrey Rake, Morris F. Shaffer, Helen P. Jones and Clara M. McKee. *Proc. Soc. Exper. Biol. & Med.*, Utica, 46: 300-303, Feb. 1941.

The authors describe a series of experiments which show clearly that the ability of Seitz EK filtrates, derived from rich suspensions of venereal lymphogranuloma virus, to fix complement specifically in the presence of lymphogranulomatous serum and to elicit a positive Frei reaction is due not to elementary bodies of the virus but to antigen in a less highly organized, possibly soluble, state. The failure of other investigators to obtain similar results is doubtless due to the low concentrations of virus present in the materials which they employed.

Observations on the inhibition of sulfonamide action by para-aminobenzoic acid. Elias Strauss, Francis C. Lowell and Maxwell Finland. *J. Clin. Invest.*, Lancaster, 20: 189-197, Mar. 1941.

During experiments involving the inhibition by para-aminobenzoic acid of sulfonamide action upon pneumococci and upon the growth of *B. coli* in human urine, the following conclusions were reached: Para-aminobenzoic acid is readily absorbed after oral administration. Maximum blood levels are reached in 1 to 2 hours after ingestion. Excretion is rapid and is practically completed in 12 hours. Some of the compound is present in conjugated form in the blood and urine. The drug is found in greater concentration in the plasma than in the red blood cells. Toxic effects of sulfathiazole therapy, as manifested by fever and rash, were neither prevented nor cured by the administration of p-aminobenzoic acid in amounts sufficient to nullify the bacteriostatic action of the drug in the blood.

Note on a possible source of error in the determination of sulfapyridine and sulfanilamide. Mary Frances Butler and Samuel B. Nadler. *J. Lab. & Clin. Med.*, St. Louis, 26: 1052-1053, Mar. 1941.

In the course of a series of sulfapyridine determinations on a patient to whom sulfapyridine was administered parenterally at a constant rate, it was observed that there was a rather marked fluctuation in the blood level of sulfapyridine. The fluctuation in blood level did not correspond to alterations in the dose or rate of administration of sulfapyridine. It was apparent, therefore, that some contaminant might possibly be responsible for the observed fluctuations. Upon inquiry it was found that it was the common practice for hospital interns to collect venous blood in syringes which had been used to anesthetize the skin with 2 percent novocaine (procaine hydrochloride) prior to venipuncture.

The color development of sulfapyridine and sulfanilamide depends upon diazoti-

zation of primary aryl amines. Procaine hydrochloride is a primary aryl amine and diazotization of its amine group with the sulfapyridine reagents are added results in a pink color which is identical tinctorial power with that obtained from sulfapyridine. As an indication of the magnitude of this source of error, it was found that after one drop of 2 percent procaine hydrochloride was added to 5 c.c. of blood a sulfapyridine value of 12.3 percent was found. There is no significant diminution in the value if the blood is allowed to stand at room temperature for 2 days.

The tinctorial power of procaine hydrochloride as compared to sodium sulfapyridine and sulfanilamide was studied, using standard 0.2 percent and 0.4 percent solutions of these substances. It was found that on an equimolecular basis the tinctorial power of procaine hydrochloride is equal to that of sulfanilamide and less than that of sulfapyridine.

PUBLIC HEALTH ADMINISTRATION

Report of public health committee.

A. Nelson. *Tr. Am. Neisser. M. Soc.* New York, 1940, pp. 56-58.

Nelson says the purpose of the Public Health Committee of the American Neisserian Medical Society is to define what it considers to be sound procedure in the control of gonorrhea in the light of recent developments in therapy and laboratory technic. The committee recommended that health officers should do everything in their power to provide facilities for the treatment of gonorrhea in public clinics, and that serious effort should be made to convince the public of the importance of gonorrhea control.

It was recommended that every State and large city laboratory should be equipped for the expert examination of stained smears; every public clinic in which gonorrhea is treated should

Equally equipped, or should have competent laboratory service immediately available. Single stain methods are entirely unreliable. It should be emphasized that this laboratory service is often inadequate and frequently erroneous. Negative smears by themselves have little or no significance, and attention should be given to careful history-taking. Positive smears from vulvovaginal infections in children must be supported by indisputable evidence of exposure to a known infection, or the diagnosis of gonorrhea should not be made without cultural confirmation. If cultural facilities are lacking, specific therapy may, nevertheless, be indicated on the basis of clinical findings and positive smears. In the adult female, if cultural facilities are lacking, positive smears must be supported by a clear history of exposure or definite clinical evidence of infection. Negative smears cannot be used as criteria of cure where any of the sulfonamides have been used. All reports of the results of examination of smears should include an estimate of the pus content in terms of the number of pus cells per oil immersion field. Until the serology of gonorrhea is improved, it is advised that its use as a routine procedure be discontinued.

The committee further recommends that health officers prepare treatment schedules for the proper use of the sulfonamides in public clinics and that clinic physicians be required to treat gonorrhea as well as syphilis. The use of sulfanilamide should be discontinued, since it is inefficient and produces many carriers. Sulfapyridine is somewhat more efficient in its rate of cure but has the same disadvantage as sulfanilamide in the production of reactions. To date, sulfathiazole has proved to be the most effective in cure and causes almost no reactions. Clinic physicians should be trained in the more complicated methods of therapy which must be used when chemotherapy fails. It should be the policy of all health departments to supply sulfathiazole to all public clinics. Whether the health department should distribute the drug to private physicians

will depend upon how well satisfied the health officer may be that he can control its use.

The operation of the premarital law in the physician's office. Fred W. Caudill. Kentucky M. J., Bowling Green, 39: 94-96, Mar. 1941.

The Kentucky premarital law became effective January 1, 1941. Based upon the results obtained under the prenatal examination law, the operation of the premarital law should disclose serologic evidence of syphilis in 1,900 to 2,000 of the 100,000 persons who apply for marriage licenses in Kentucky annually. From June 12, 1940, when the prenatal examination law went into effect, until Nov. 22, 1940, 1.9 percent of the pregnant women examined had positive serologic reactions. This means that in a year, during which about 60,000 children are born in Kentucky, approximately 1,100 women would be found who are syphilitic.

The responsibility for making the diagnosis of syphilis in marriage license applicants rests upon the examining physician. He must make a thorough and careful examination of the applicant, and he should keep a record of these findings in case there should be a question as to his diagnosis. When he receives the confidential report from the approved laboratory which has examined the blood specimen from the applicant, he must combine this report with his findings to establish his diagnosis. If syphilis in a communicable stage is found, the certificate is withheld, the case is reported to the health department of the county or city in which the applicant resides, and the applicant is advised to begin treatment at once. The minimal treatment shall consist of 20 doses of an appropriate arsenical and 20 doses of a heavy metal. There are certain problem cases in which the certificate must be withheld until the question of communicability has been determined by the examining physician and the proper health official.

The county court clerk may issue a marriage license without a medical certificate after a hearing has established (a) that the female applicant is pregnant and marriage is necessary to confer legitimacy on her unborn child; (b) that the applicant has syphilis in a stage not communicable; (c) that the applicant does not have syphilis in any stage.

Syphilis by census tracts. Distribution of cases of syphilis treated in hospital out-patient departments, March 1939. Howard Whipple Green. Joint Social Hyg. Comm. of Acad. of Med. of Cleveland and Cleveland Health Council, 1940, 20 pages.

The author presents the findings of a survey of cases of syphilis treated in hospital out-patient departments in Greater Cleveland (Cuyahoga County), Ohio, in March 1939. Families in the county were not distributed uniformly—65 percent lived east of the Cuyahoga River and 35 percent lived west of the river. However, 87 percent of the county's syphilitic patients lived east, while only 13 percent lived west of the river. Ninety-six percent of these patients lived in the area in which 71 percent of the county's families lived.

There were 8 cases of syphilis per 1,000 families in the county; 11 per 1,000 families east, but only 3 per 1,000 families west of the river. In 21 of the 341 census tracts of Cuyahoga County, there were 50 or more cases per 1,000 families, but in other census tracts there were no cases.

The total number of cases was 2,640, of which 529 (20 percent) were infectious. Of the 529 infectious cases, 24 percent were white patients and 76 percent Negroes (497 lived east but only 31 lived west of the river).

Twenty percent of the patients traveled less than 1 mile for treatment; 32 percent, 1 to 2 miles; 23 percent, 2 to 3 miles; 13 percent, 3 to 4 miles; 6 percent, 4 to 5 miles; and 4 percent, 5 miles or more.

The author presents the statistical data in 2 tables and 10 statistical maps of Greater Cleveland.

The incidence of neurosyphilis, especially parasyphilis. C. W. Botte. *Nederl. tijdschr. v. geneesk.*, Haarlem 84: 4272-4276, Nov. 2, 1940.

The author reports on the fate in regard to the development of neurosyphilis and parasyphilis of a total of 1,470 syphilitic men in the Dutch Navy. The period of observation of this group was the last 30 years, and during this time careful examinations were made including clinical, roentgen-ray, electrocardiographic and spinal fluid and blood serologic examinations. Careful records of the findings and of the treatment given were sent to a central office where the records were filed on cards. After treatment had been completed, blood serologic examination was made in the second or third year, and once in a 5-year period a complete physical examination was made. The patients were observed for a period varying from 5 to 20 years. A table which shows the results of the survey is given. The patients are divided according to type and amount of treatment received and length of period of observation.

Among a group of 144 patients who received no antisyphilitic treatment, 11 percent neurosyphilis developed in those observed for 5 to 10 years in 14 percent, parasyphilis in 8.3 percent; in those observed for 10 to 15 years neurosyphilis developed in 17.7 percent, parasyphilis in 13.2 percent; in those observed for 15 to 20 years neurosyphilis developed in 18.5 percent, parasyphilis in 7.4 percent.

Among a group of 466 patients treated with mercury, neurosyphilis developed in those observed for 5 to 10 years in 13 percent, parasyphilis in 3.6 percent; in those observed for 10 to 15 years neurosyphilis developed in 11.6 percent, parasyphilis in 3.9 percent; in those observed for 15 to 20 years neurosyphilis developed in 15.6 percent, parasyphilis in 4 percent.

Among a group of 357 patients who received only a small amount of treatment with arsphenamine, neurosyphilis developed in those observed for 5 to 10 years in 3.2 percent, parasyphilis in 0

percent; in those observed for 10 to 15 years neurosyphilis developed in 11 percent, parasyphilis in 3.4 percent; in those observed for 15 to 20 years neurosyphilis developed in 8.3 percent, parasyphilis in 0 percent.

Among a group of 503 patients who received intensive arsphenamine treatment neurosyphilis developed in those observed for 5 to 10 years in 0.03 percent, parasyphilis in 0.0 percent; in those observed for 10 to 15 years neurosyphilis developed in 0.6 percent, parasyphilis in 0 percent; in those observed for 15 to 20 years neurosyphilis developed in 1.7 percent, parasyphilis in 0.0 percent.

Venereal diseases in war. M. Schubert. Med. Welt, Berlin, 14: 1037-1040, Oct. 12, 1940.

A comparison is made between the incidence of venereal diseases in the Prussian Army during the prewar period from 1908 through 1913 in which the average incidence was 20.4 per thousand and that of the 4-year period of the World War in which the average incidence was 20.5 per thousand. Contrary, therefore, to the widely prevalent but false assumption that at the World War incidence of venereal disease was much higher than in times of peace, the difference is very slight. The only unfavorable finding was that the increase which did occur was an increase in the number of cases of syphilis. Of those who became infected during the war, 65 percent contracted the infection at home and only 32.5 percent at the front. Following demobilization of the Army after the war, with its tragic circumstances, there was a catastrophic increase in the incidence of venereal diseases up to the years 1921-22, following which there was a gradual decrease which in 1925-26 came increasingly noticeable. This decrease was probably due to better regulated conditions for treatment. In 1919 a total of 528,000 persons had recent infections with venereal diseases, in 1927 there were 323,000 and in 1934 there were 9,000. The decrease in the incidence of syphilis was greater than that of gonorrhea. During the past few years chan-

roid has been very rarely seen in Germany. In the Navy the incidence before the war was 45 per thousand, in 1923 it was 104 per thousand, in 1934 it was 18 per thousand, and in 1937 it was 19 per thousand. This decreased incidence is attributed largely to the compulsory use of prophylaxis. During the period from 1918 to 1923 the use of prophylaxis was optional but since 1923 it has again been compulsory.

During the first 9 months of the present war no increase in the incidence has been observed except among the troops who had been in Poland, and among them the number of syphilitic infections was low. Chancroid was not found.

Preventive measures consist of education of the civilian population as well as the enlisted men regarding venereal diseases. In the Army this is done as much as possible in connection with periodic physical examinations. The use of prophylaxis before and after sexual contact should be emphasized. Thorough physical examinations should be given to new soldiers and to those returning from furlough in order to find concealed infections. Great effort should be made to trace sources of infection. Each infected person has to fill out a form in regard to the source of infection which includes a detailed description of the person. Sources of infection are traced and are carefully examined. Since September 1939, women working in places of amusement have to submit to periodic examinations. Prostitutes are controlled as they were formerly, and sexually promiscuous women also are reported to the military authorities.

Chemotherapy of gonorrhea is the treatment of choice. It has the advantages over methods formerly used that it is simpler and that its use results in fewer complications, and the disadvantage that it produces side effects. By the end of 1939 the author had treated 1,740 cases of gonorrhea with various sulfonamide preparations. With two courses of treatment separated by 5 to 6 day rest periods, 90 percent of cures were obtained.

The law for the campaign against venereal diseases. Sozialhyg. d. Geschlechtskr., Berlin, No. 1, Feb. 1941.

The following changes in or additions to the law of February 18, 1927 for the campaign against venereal diseases were made in October and November 1940:

Anyone with a venereal disease in the infectious stage who is unable to pay for treatment shall receive free treatment at public expense.

Instead of the law definitely stating that certain houses or blocks of houses in a street cannot be used for prostitution, it now states that the health authority in regard to this law rests with the health department.

Any health insurance physician (health insurance is compulsory in Germany) may treat venereal diseases. He has to furnish an initial report as well as a summary of the case at the end of treatment to the health department.

All persons who are known to be sexually promiscuous are to be kept under strictest control and observation. It is suggested that examinations be made once a month or once every 3 months, depending on the habits of the person under observation and that observation by private physicians should not be permitted if the person changes physicians more than twice a year.

Each person who knows or who under the circumstances should know that he has a venereal disease must seek treatment and continue treatment without interruption until he is discharged by his physician. If necessary, he is forced to do so with the help of the police. It is the physician's duty to report to the health department all cases lapsing from treatment or refusing treatment for venereal disease.

Every person (1) who knows or who under the circumstances should know that he has a venereal disease in the infectious stage, yet has sexual intercourse,

(2) who deliberately opposes the regulations for the control of venereal diseases according to the law,

(3) who makes available substance for self-treatment for venereal disease is punished with imprisonment for years or a fine of 3,000 gulden.

Any physician who deliberately sends in an incorrect report to the health authorities in regard to the physical condition of a person or who deliberately permits a venereal disease to be spread is punished with imprisonment from 1 month to 2 years.

All prostitutes in large cities are compelled to undergo a physical examination by a physician for skin and venereal diseases every seventh day. The physician reports his findings on a certificate to the health department and records the examination in the control-book of the prostitute, by means of which the health authority is informed whether the prostitute is being examined regularly. If she fails to do so, compulsory measures are used. One physician who since 1936 continued to issue certificates to the health department and to make entries in the control-books of prostitutes without having made examinations, yet charged the usual fee for his services, was sentenced to 8 months imprisonment. His appeal to the Reich court was denied.

If a married person has concealed the fact that he has a syphilitic infection from his marital partner, this is cause for divorce unless the partner has expressed the intention, after knowing of this infection, that he does not want a divorce or unless certain conditions in the marital relationship would make this morally unjustified.

Women under control of the health authorities who were regularly examined at the University Polyclinic for Skin Diseases in Leipzig in the years 1937 to 1939. H. Gottschalk. Sozialhyg. d. Geschlechtskr., Berlin, No. 4, pp. 24-27, July 1940.

Altogether 342 women were under control of the health authorities during the 3 years 1937 to 1939 and were examined periodically at the University Polyclinic for Skin Diseases in Leipzig. In January 1937 there were 170, in January 1939

ere were 131, in January 1939 there ere 133 and in December 1939 there ere 53 women under control. This de- ease in the number was due to the fact at many of the women were referred private physicians.

In regard to age, 5.2 percent of the 342 ere 20 years old or younger; 28.6 per- cent were 21 to 25; 24.2 percent were 26 to 30; 16.0 percent were 31 to 35; 11.8 percent were 36 to 40; 9.0 percent were 41 to 45; 4.4 percent were 46 to 50; 1.2 percent were 51 years old and older.

The number of observations was not e same for all women, some being ob- served as often as twice a week and hers only once a month, a few having en observed only once every 3 months. During this 3-year period gonorrhea as diagnosed 159 times, primary and condary syphilis with manifestations times, early latent syphilis 14 times, te latent syphilis 8 times, and tertiary philis once. The average yearly per- centage was 26.4 for gonorrhea, 1.0 for imary and secondary syphilis with anifestations, 2.3 for early latent syph- s. The author states that in com- rison to the findings in other large ies, these figures are favorable. When culated on the basis of 12 months of servation (one examination per month) ead of on the basis of the actual mber of observations made during e year which was usually less, the per- centages are gonorrhea 42.1, primary and econdary syphilis with manifestations 3.1, and early latent syphilis 3.7.

Syphilitic patients treated during the year 1939. G. González Peris. *Vida Nueva*, Habana, 47: 81-89, Feb. 1941.

In the department of dermatology and philology of the University of Habana 292 patients were seen during 1939 of whom 530 (24.2 percent) were diagnosed as having syphilis. This corresponds very esely to the findings of 1938 when 2,216 ients were seen of whom 24.36 percent ere syphilitic. Among those with syphi- l 25.15 percent had latent untreated hphilis, 24.3 percent had early syphilis, 4.6 percent had congenital syphilis, 4.5 per-

cent had neurosyphilis, and the remain- der had manifestations of late syphilis. Only 5 patients with involvement of the heart or aorta were seen during the year. The greatest percentage of cases of syph- ilis occurred between the ages of 21 and 30 years (31.6 percent), next between 31 and 40 years (26.7 percent). Grouped according to race, there were 489 Cubans, 25 Spaniards, 8 Chinese, 4 Englishmen, 1 Mexican, 1 North American, 1 Turk, and 1 Japanese among the syphilitic patients. The drugs used in treatment were neoars- phenamine, mapharsen, solusalvarsan, and bismuth.

The defense program to date: An ap- praisal. Richard H. Anthony. *Bull. Massachusetts Soc. Social Hyg.*, Bos- ton, 11: 3, Mar.-Apr. 1941.

In Massachusetts military establish- ments during the 6 months ending Dec. 26, 1940, 328 promiscuous sexual contacts were reported in a total of 6,347 men. The total Army personnel in Massachusetts on April 1, 1941, was approximately 50,000. Very few syphilis cases had been con- tracted by the troops, and of those re- ported less than a half dozen are traceable to contacts in the State. Of 96 gonorrhea cases visited by a State nurse-epidemiolo- gist in early March, 38 were traceable to contacts within the State. There is no evidence that the concentration of soldiers has, of itself, affected the rate of inci- dence of syphilis and gonorrhea in this State.

Prevention of conditions likely to result in the spread of genitoinfectious diseases, aside from treatment and follow-up work, falls into the 2 categories of repression of prostitution and minimizing opportunities for promiscuous relationships, and the provision of wholesome recreational ac- tivities for enlisted men on leave. The Federal Government, the State, the com- munities, and voluntary organizations are attacking the problem from both angles. Congress is considering an appropriation of \$150,000,000 to be expended in activities related to the defense program, and of this, \$15,000,000 is to be used for the erec- tion of recreation centers. The State di-

vision of genitoinfectious diseases has expanded its program to cover follow-up work in communities. Mayors' committees are forming to undertake recreational programs for soldiers on leave. Six voluntary agencies have banded together as United Service Organizations, Inc., and are planning a national campaign to raise \$10,750,000 for the purpose of administering recreation centers erected by the Government.

Teaching about the venereal diseases in a California High School. Anita D. Laton. *J. Social Hyg.*, New York, 27: 76-77, Feb. 1941.

Each year a large number of student teachers work at the University High School in Oakland, California. Biology and physiology are offered as electives in science and are taken by approximately a third of the students. A unit of communicable diseases is included in each of these courses, and study of the social aspects of communicable diseases is included in some of the social studies classes.

At the beginning of the year the students and the teacher discuss what should be included in the study of communicable diseases, and the teacher calls attention to bulletins published by the State health department and by the U. S. Public Health Service. The teacher sees that syphilis and gonorrhea are included in the course, among probably 10 other diseases. Often one student or a small group becomes responsible for teaching the rest of the class about the disease, the teachers supervising reports. The venereal diseases are emphasized in the same way as other diseases for their costliness in lives, in health, efficiency, happiness, and money.

This program of instruction has been in operation for more than 20 years and has always been favorably received. It is not easy to estimate how valuable any instruction in venereal disease can be which fails to reach the whole student body. The percentage of the student

body that is reached in this school is large enough to remove the assumption that the venereal diseases are not subjects for study or discussion. Students compare notes informally, and there is general knowledge as to what is being studied in various classes. Books containing information about all the communicable diseases are available on open shelves. It is felt that a wholesome attitude is being well achieved by this program.

Incidence of syphilis among college students. Robert A. Greene, Edward Breazeale and J. E. Andes. *Southwestern Med.*, El Paso, 25: 46, 47, Feb. 1941.

Since the fall of 1938, a serologic test for syphilis has been included as a part of the physical examination for all new students at the University of Arizona. Previously, approximately 1,000 blood specimens had been submitted principally from students working as food handlers or in connection with the cooperative dormitories. Between 1936 and 1940, 5,000 specimens have been received from students. Of these, 98 percent gave negative reactions and 0.4 percent (20) positive reactions. On the basis of repeated laboratory tests and thorough examination only 6 students were diagnosed as syphilitic, an incidence of 0.12 percent. There were 83 students who gave doubtful or positive reactions but were considered nonsyphilitic after repeated study and thorough examination.

In general, the nonspecific reactions were associated with students who were suffering from chronic diseases, those who had gone to Tucson for reasons of health.

The doubtful serologic group contained a slightly higher incidence of students suffering from sinusitis, tuberculosis, bronchial asthma than did the entire group but these were not significant. However, there was a threefold increase in the prevalence of leukorrhea among the female students with nonspecific reactions as compared to the females who gave negative serologic results.

Editorial notes. J. Indiana M. A., Indianapolis, 34: 217, Apr. 1941.

The American Social Hygiene Association recommends that appropriate recreational facilities be provided immediately adjacent to the camps where civilian inmates are located. The recommendation is based on the theory that these young men will seek some sort of diversion in their periods "off duty," and that such facilities will do much to keep down the incidence of venereal disease among this group.

The Peru (Indiana) Tribune has said, "Men in barracks are no more plaster saints than they were in Kipling's day. Released from heavy army duties, they will have fun; and if opportunities for decent, wholesome fun are lacking, they will seek whatever kind is available."

Syphilis is a family health problem. Alice M. Kresge and Alice Malcolm. Pub. Health Nursing, New York, 33: 55-58, Feb. 1941.

The nurse in a generalized nursing service who is alert to the problems in the families has a valuable contribution to make in the control of syphilis and gonorrhea. The staff of the Public Health Nursing Association of Pittsburgh have long done health teaching in this regard. The care and teaching necessary in the home where there was a patient with one of these diseases have been an integral part of family health work. Two years ago the genitoinfectious disease service became one of the recognized services in the generalized program, with a part-time social hygiene supervisor. A new family record form was set up to facilitate the staff nurse in helping the family. This placed the service in the same category with the other services of child health, maternity, nutrition, and tuberculosis.

Follow-up service is available for private physicians and hospital clinics. The nurse acts as a case-holder and a case-finder in instances where there is no other agency to render this service. The follow-up and examination of contacts are usually the responsibility of the nurse

visiting in the home. Patients and contacts are visited only until they are well established under medical supervision; then they are dismissed to that source of supervision, except in families where there are other health problems requiring the service of the nurse. If a patient later fails to report for treatment, the nurse may be called upon to make further home visits.

Most of the patients under the supervision of the association first came to the nurse's attention through some other service she was giving in the home, principally antepartum health supervision. The nurse who is constantly alert often contributes to this program in numerous instances during her regular work. Although the genitoinfectious disease service has been made a distinct service with its own special record, it is through the general family health work that the greatest gains are made.

Two such instances are described by the authors.

Survey shows high ethics among druggists. J. Social Hyg., New York, 27: 85, Feb. 1941.

The Social Hygiene Society of the District of Columbia submits new proof of the effectiveness of its efforts to secure cooperation from local pharmacists in regard to over-the-counter prescribing. As in previous years, the Social Hygiene Society arranged for a young man to visit drugstores in all sections of the city and ask advice for a supposed infection. In a majority of the 112 drugstores visited, the pharmacists urged the youth to consult a physician as soon as possible. Some recommended certain doctors, all of whom were found to be in good standing.

An attempt was made at each store to buy sulfanilamide, but only two drug clerks were willing to sell it without prescription. Of all the stores visited, only 5 were willing to prescribe for gonorrhea, and none for syphilis, showing an improvement over last year, when 15 drugstores were found to indulge in counter-prescribing.



Conference of State and Territorial Health Officers

May 1-2, 1941

THE FOLLOWING statements were presented by the Committee on Venereal Disease Control at the Conference of State and Territorial Health Officers, and after consideration they were adopted by the Conference on May 1, 1941.

A plan to insure adequate venereal disease control measures for personnel discharged from the United States Army, Navy, and Coast Guard.

The rigid physical requirements of the Medical Corps of the United States Army, the Bureau of Medicine and Surgery of the United States Navy, and the United States Public Health Service make it possible for the Army, the Navy and the Coast Guard to select from the civilian population men for service who are not infected with the venereal diseases. State and local departments of health have been cooperating with these Federal agencies to aid in this selection of a healthy armed force and to insure the organization of an effective venereal disease control program in all areas where such personnel are concentrated.

Under the Selective Service System more than a million men will be inducted in the Army each year for the next 5 years. After the end of the first year of service approximately 1,000,000 men will be separated from the Army each year. These large numbers do not include the enlisted personnel which serve in the Army, the Navy, and the Coast Guard. In spite of the most effective venereal disease control program which

can be developed under existing conditions, it is certain that a considerable number of these men will be infected with the venereal diseases during their service period. The members of the Conference of State and Territorial Health Officers therefore recommend to the Secretary of War, the Secretary of the Navy, and the Federal Security Administrator the following plan to insure the adequate treatment of men infected with the venereal diseases in the military services and to prevent the transmission of such diseases by these men upon their return to civilian life.

1. A thorough physical examination to detect the venereal diseases, including a serologic blood test for syphilis and including also, if clinically indicated, necessary microscopic examinations of smears and culture examinations for the detection of the gonococcus, on each man before his discharge from the military services.
2. The administration before discharge of a minimum of 20 doses of one of the trivalent antisyphilitic arsenical drugs and 20 doses of one of the heavy metals by the medical corps of the respective military service to each man found to be infected with syphilis.
3. The administration before discharge from the military service of two grams of sulfathiazole per day for 10 successive days to each man found to be infected with gonorrhea.
4. The adequate treatment before discharge of all men found to be infected with chancroid, granuloma inguinale, and venereal lymphogranuloma to insure that such infected men

are rendered incapable of transmitting their infections to others.

5. Before discharge from the military service of any man infected with the venereal diseases, the responsible medical corps should communicate with the health department of the State to which the infected man expects to proceed, to obtain from the State health officer assurance that free treatment facilities will be available at his new place of residence.
6. If no health department facilities for the free treatment of such infected man are available, the man should be retained by the respective medical corps until there is reasonable assurance that he has recovered from his infection.

II. Treatment of Selectees Infected with Gonorrhea After Induction

Whereas selectees called under the Selective Service Act and found to have uncomplicated gonorrheal urethritis are not accepted for induction into the United States Army; and

Whereas this policy results in turning back into the civilian population infected persons by whom the infection may be spread; and

Whereas modern methods of treating this disease result in prompt cures in a high proportion of cases; Therefore be it

Resolved, That it is the opinion of the members of this Conference that the objectives of the Selective Service Act and the health and welfare both of persons called for service thereunder who are found infected with uncomplicated gonorrheal urethritis and of the civilian public, could best be served if such selectees were promptly inducted into service and treated; and be it further

Resolved, That the members of this Conference recommend such action and that copies of this resolution be sent to the proper officials of the War Department and the Selective Service System.

III. Revision of the Regulations Requiring Cooperation of Local Law Enforcement Authorities in the Repression of Prostitution before Federal Funds Reallotted to Local Health Departments for the Control of the Venereal Diseases

The members of the 38th Annual Conference of State and Territorial Health Officers approved on May 9, 1940, recommendations for the repression of prostitution. These recommendations described the important relationship which tolerated and segregated prostitution bears to the spread of the venereal diseases, and defined the responsibility for the application of repressive measures.

Since this formal action by the members of the Conference, the prostitution problem in the United States has become even more grave. This is particularly true in those areas where armed forces or national defense workers are concentrated. In some such areas recent studies have indicated the presence of prostitutes equivalent in number to one percent of the population. Under such conditions, so great is the number of exposures of men and boys to infected or potentially infected prostitutes that there is grave danger that venereal disease rates will increase greatly.

In those areas where prostitution is tolerated and segregated, the problem, since a venereal disease control program has been organized utilizing State and Federal aid, that toleration of prostitution and an effective venereal disease control program are compatible. All health authorities know, to the contrary, that the greater the number of sexual contacts of healthy people with infected persons, or those harboring the spirochete or gonococcus, the higher will be the incidence rates for syphilis and gonorrhea. Certain members of the local police and local health authorities may distort the facts either through ignorance or political considerations because of a desire to participate illegally in the financial benefits derived

om this vice. To encourage the repression of prostitution because of its public health importance and to inform public-spirited citizens of the incompatibility of tolerated prostitution and effective venereal disease control measures, the following revision of Section XV, paragraph 7, of the Regulations Governing the Allotment and Payment of Venereal Disease Control Funds is adopted by the members of the Conference:

7. In reallocating funds under this act for local venereal disease control services, the State health officer shall give due consideration to the relatively higher prevalence of syphilis and gonorrhea in urban areas, *provided that after conference with the local health officer the State health officer shall require from the agency of local government responsible for law enforcement against prostitution within the area a written statement that during the period when Federal funds are made available a program of repression of prostitution will be enforced. This statement from the director of the agency of the local government responsible for law enforcement against prostitution shall certify that during the life of a local venereal disease control budget, which includes Federal funds, such law enforcement authority will vigorously enforce all local and State laws prohibiting prostitution, procurement, solicitation, and assignation. Failure of the responsible authority to enforce such laws during the life of the venereal disease control budget will disqualify the local health department for further reallocations of Federal funds for venereal disease control work until satisfactory proof is produced by such local authority that said laws are actually being enforced.*

An Administrative Plan for the Venereal Disease Control Program

In considering appropriations for the control of the venereal diseases, the United States Congress has requested that the Public Health Service make a

careful study of the administrative costs of the venereal disease control program in the States and work out an acceptable plan of venereal disease control administrative practice with the health officers of the respective States. The Congress has further expressed the desire that these administrative costs, including both State and Federal funds, be limited as far as is consistent with the prosecution of an effective venereal disease control program.

A careful study of administrative costs for venereal disease control work has been completed by the Public Health Service and a uniform plan is described. This plan includes provision of the following personnel and services.

1. The State venereal disease control officer. The travel allowance of such officer should not be included as an administrative item because, in most States, this officer performs some duties connected with field work.
2. The clerical assistant to the venereal disease control officer. The clerical assistant should perform those duties pertaining to the venereal disease control officer's correspondence, filing, or other general office work in this section of the health department.
3. All other clerical or stenographic personnel at the State level, provided the major portion of their activities is concerned with general office work under the immediate supervision of the State venereal disease control officer. This item includes personnel concerned with the accounting of funds, but excludes personnel concerned with statistical activities since the latter are included in the category of personnel performing duties connected with consultation and dissemination of technical information.
4. All activities concerned with the administration of the merit system on the State level.

The total administrative costs of a State program for the control of the

venereal diseases vary according to the population, the size of the State, and the cost of government in States with a large area and relatively sparse population. In general, however, it is recommended that the total cost of administration of the venereal disease control program shall not exceed 5 percent of all funds expended for this phase of public health work in States with a population greater than one million, and 10 percent in States with a population of one million or less.

V. Reciprocity between States in Premarital Examinations to Detect Syphilis

There are, at present, a total of 24 States in which statutory provisions have been enacted requiring premarital blood tests for syphilis. It is, therefore, expedient to render compliance with the provisions of these statutes as free from inconvenience to the general public as is consistent with the duty which is imposed.

A very distinct inconvenience is frequently caused to prospective marital partners who reside in widely separated jurisdictions. In such instances it may be necessary for each party to proceed to the place at which the necessary legal formalities are to be complied with at a date sufficiently antedating the actual ceremony to permit a report of test findings to be secured. This time interval may be a week or longer. Much of this unjustifiable inconvenience could be obviated through the institution of free and full reciprocity between the various States or in those States in which the wording of the enactment does not specifically provide that the blood serologic test be performed in the laboratory of the State in which the legal ceremony is to take place.

In support of a plea for free reciprocity in premarital blood testing it is the expressed opinion of the Committee on Evaluation of Serodiagnostic Tests for

Syphilis that an entirely satisfactory level of efficiency in the conduct of serologic tests has been attained by practically all State laboratories and that such laboratories may be depended upon to supply a finding which is considered accurate within the limitations of methods which are at present in general use. On this basis the acceptance of serologic reports from the various States would not in any way detract from the social value of the enactments and would result in a marked reduction in inconvenience at present imposed upon applicants for marriage licenses in jurisdictions other than that of the residence.

It is realized that reciprocity in premarital serologic examinations is definitely interdicted by the wording of the statutes in certain States. In other States, especially in those in which the actual operation of the provisions of the law is placed under the guidance and supervision of the health departments, a program of full and free reciprocity would seem to be entirely feasible. A liberalization to this degree would serve to prevent unjustifiable antagonism toward the measures, a circumstance which is always detrimental to the advancement of social progress.

It is therefore recommended that several State health officers administering the laws requiring premarital examinations including serologic tests for syphilis reciprocate with all State and local laboratories in those States where the Surgeon General of the Public Health Service, after consultation with the Committee on Evaluation of Serodiagnostic Tests for Syphilis, certifies as being approved for the performance of such serologic tests. Such full reciprocity should be extended by the States wherever the procedure is not specifically interdicted by the wording of the State statutes.

Reciprocity should also be furthered by the delegation of broad powers to State health departments in matters pertaining to the practical administration of the enactments of premarital legislation under advisement at this time.

Syphilis-Malaria Survey, Onslow County, North Carolina

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THE VENEREAL disease program in the State of North Carolina was given considerable impetus in the fall of 1937 by a gift of \$100,000 from the Zachary and Reynolds Foundation. In 1938 additional financial assistance was received from the United States Public Health Service. As a result of this financial aid, the venereal disease control program was under way without an abundant knowledge of the exact prevalence of the venereal diseases in the State. Clark (1) reported that 11.8 percent of the 10,198 Negroes in Pitt County, North Carolina examined in 1931 had positive Wassermann reactions. Other smaller and scattered surveys in the State showed from 15 to 30 percent positive reactions.

Malaria is very prevalent in some sections of North Carolina and many health officers and private physicians have noted discrepancies in their serologic reports, especially in malarious areas during the malaria season. It is apparently a well-established fact that malaria can give false positive reactions to serologic tests for syphilis. Several of the health officers in North Carolina have at times secured a blood smear for malaria examination and a blood specimen for serologic examination at the same time. Most of them used blood obtained from vein for both tests. The results have been unsatisfactory and not enough specimens have been secured to draw conclusions.

This survey was carried on, therefore, for the purpose of determining the prevalence of syphilis and malaria in a given area and the effect of malaria on the

serologic report as sent out from the laboratory. We have not attempted to show the variations in the different serologic tests. Additional data which we secured are also presented.

Syphilis control in North Carolina is primarily a problem of control among the Negro race. About 90 percent of persons reported as having syphilis and patients under treatment for syphilis belong to this race. We have, therefore, confined our study to Negroes only.

A county in the eastern or malarious section of the State in which little effort had been made to reduce the prevalence of either syphilis or malaria, was considered appropriate for our survey. Accordingly, it was decided to select a county that had never had an organized health department and was not surrounded by counties that did have.

Onslow County was finally selected as most nearly meeting our criteria.¹ This county borders on the Atlantic Ocean, is about half way from the northern to the southern border of the State, and abounds in marshes and small streams. The county contains 743 square miles and had a total population of 15,289 in 1930 or 20.6 persons per square mile. There were 4,079 Negroes enumerated in this county in 1930, or 26.6 percent of the total. The county is entirely rural, the largest town having a population of approximately 800. Most of the residents

This study was made possible by funds granted by the United States Public Health Service to the North Carolina State Board of Health.

¹ A full-time health department was organized in Onslow County, January 1, 1941.

are engaged in farming and are not inclined to move about a great deal; in fact, over 88 percent of the Negro population have had no more than two different residence in the past 5 years.

The securing of blood samples was carried out between August 1, 1939 and April 1, 1940. A Negro physician and nurse obtained all blood specimens and filled out the questionnaire. They resided in the county during the entire survey. A house-to-house canvass was made in order to get as many as possible of all Negroes residing in the county. In addition, blood specimens were taken at schools, churches, picnics, or wherever a crowd congregated. Approximately 80 percent of the entire population was tested. The county was divided into 18 districts so that we could secure the geographic distribution of both syphilis and malaria.

Venous blood was secured for the serologic test, and a finger puncture was made in order to secure a "thick smear" for the malaria examination. All serologic specimens were examined by the Kline diagnostic test. Those serums which gave positive and doubtful reactions with this test were also examined by the Eagle complement fixation test. These tests were performed by the North Carolina State Laboratory of Hygiene. Malaria smears were stained by the Giemsa technic and examined by a skilled technician.

When the laboratory reported positive or doubtful serologic reactions for syphilis or the presence of malaria parasites, an additional specimen was secured and the tests repeated. Intervals between tests varied generally between 6 and 10 weeks. In some instances where there was a discrepancy between the results of tests, as many as four specimens were taken from one person. All repeat tests included serologic tests for syphilis and search for malaria parasites. Tests were also repeated whenever hemolysis or breakage occurred.

A questionnaire was filled out for each person tested. This contained in-

formation which we considered might throw some light on the possible relationship of syphilis to malaria.

RESULTS OF SEROLOGIC SURVEY

Age, Sex, Marital Status.—A total 3,244 individuals were tested. There were 1,451 males and 1,793 females in the group. The age and sex distribution of the population surveyed, with results of serologic tests for syphilis and examinations for malaria parasites are shown in table 1. The marital status of the group was approximately as follows: Single, 66 percent; married, 29 percent; widowed, 4 percent; separated, 1 percent; divorced, 0.1 percent.

Serologic Findings.—Of the 3,244 persons tested there were 2,760 (85.1 percent) who were serologically negative on the first test. Only the malaria patients were retested in this group. There were 585 specimens that gave either positive malaria findings or positive or doubtful serologic findings, and 511 of these were retested one or more times. Ninety-five percent of all individuals with a positive or doubtful serologic reaction had two or more tests. We were able to make a final serologic classification of all persons as follows: Positive, 9.9 percent; doubtful, 5.0 percent; negative, 85.1 percent (tables 1 and 2).

These tables show that the prevalence of syphilis in the Negro population of Onslow County, North Carolina, is somewhat lower than in other similar groups. Crabtree and Bishop (2) reporting from Tennessee and Burney (3) from Georgia found approximately 26 percent positive serologic reactions in each area. Walker, Haney and Ricks (4), working in Mississippi, secured results more nearly approximating ours—7.1 percent. The results obtained by Maxcy and Brumfield (5) in a survey carried out in Virginia correspond closely with ours—9.7 percent.

Age and Sex Distribution.—The age and sex distribution of our cases with positive and doubtful serologic reactions is shown in table 1. Females averaged

1.2 percent positive reactions while the male average was 8.3 percent. However, in the age groups above 30, the males alternated with the females in percentage of positive serologic reactions. The higher percentage of doubtful reactions in the younger age group is be-

lieved to be due to the fact that this group shows the greatest malaria prevalence. In the oldest age groups the doubtful reactions again increase which may be accounted for by the accumulated treated and untreated syphilitics in this group.

TABLE 1.—*Serologic and malaria findings by age groups and sex*

Sex	Age group	Malaria		Serologic results						Total	
				Positive		Doubtful		Negative			
		Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
Male	Under 1 year	---	0.0	1	20.0	---	0.0	4	80.0	5	100.0
	1-4 years	5	2.8	3	1.7	2	1.1	173	97.2	178	100.0
	5-9 years	16	5.4	14	4.8	17	5.8	263	89.4	294	100.0
	10-14 years	13	4.4	8	2.7	20	6.7	270	90.6	298	100.0
	15-19 years	8	4.0	10	5.0	3	1.5	186	93.5	199	100.0
	20-24 years	3	3.5	8	9.3	5	5.8	73	84.9	86	100.0
	25-29 years	1	1.3	12	15.4	4	5.1	62	79.5	78	100.0
	30-34 years	2	3.7	18	33.3	1	1.9	35	64.8	54	100.0
	35-39 years	1	2.2	9	20.0	---	.0	36	80.0	45	100.0
	40-44 years	---	.0	8	25.8	---	.0	23	74.2	31	100.0
	45-49 years	---	.0	4	9.8	3	7.3	34	82.9	41	100.0
	50-54 years	1	2.9	10	29.4	3	8.8	21	61.8	34	100.0
	55-59 years	---	.0	5	20.0	---	0.0	20	80.0	25	100.0
	60 years & over	---	.0	10	12.0	3	3.6	70	84.4	83	100.0
	Total	50	3.4	120	8.3	61	4.2	1,270	87.5	1,451	100.0
Female	Under 1 year	---	.0	---	.0	---	.0	4	100.0	4	100.0
	1-4 years	3	1.9	6	3.7	6	3.7	149	92.5	161	100.0
	5-9 years	10	2.9	19	5.5	31	9.0	293	85.4	343	100.0
	10-14 years	10	3.6	13	4.6	15	5.3	253	90.0	281	100.0
	15-19 years	12	5.0	17	7.1	14	5.9	208	87.0	239	100.0
	20-24 years	4	2.7	27	18.0	6	4.0	117	78.0	150	100.0
	25-29 years	3	2.4	29	22.8	4	3.1	94	74.0	127	100.0
	30-34 years	2	2.0	19	18.8	7	6.9	75	74.3	101	100.0
	35-39 years	3	3.3	26	29.0	2	2.2	62	68.9	90	100.0
	40-44 years	---	.0	10	17.2	4	6.9	44	75.9	58	100.0
	45-49 years	2	3.5	13	22.8	3	5.3	41	71.9	57	100.0
	50-54 years	---	.0	7	13.0	2	3.7	45	83.3	54	100.0
	55-59 years	---	.0	9	19.6	1	2.2	36	78.3	46	100.0
	60 years & over	2	2.4	6	7.3	7	8.5	69	84.1	82	100.0
	Total	51	2.8	201	11.2	102	5.7	1,490	83.1	1,793	100.0

TABLE 2.—*Comparison of the serologic results of persons with malaria, with a history of malaria, and without either*

	Serologic results							
	Positive		Doubtful		Negative		Total	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
With malaria	11	10.9	24	23.8	66	65.3	101	100.0
With history of malaria	156	14.2	61	5.6	877	80.2	1,094	100.0
Without either	154	7.5	78	3.8	1,817	88.7	2,049	100.0
Total	321	9.9	163	5.0	2,760	85.1	3,244	100.0

Geographic Distribution.—A wide variation in the serologic findings was noted in the different districts (table 8). The percentage of persons with positive sero-

logic reactions in the different districts varied from 0 to 23. The residents of district number 8, where we found no positive reactions, are reported to be very

moral. District number 2, where we found the highest percentage of positive reactions, 22.7, is practically isolated from other parts of the county. The people seldom get to town but mingle freely in their own group. One can surmise, however, that several cases of infectious syphilis have no doubt found their way into this district.

The town of Jacksonville is located in district number 6 and Richlands in district number 2. Neither of these towns shows a much higher than average incidence of positive serologic reactions.

The population of the county is very stable; 90.6 percent of the positive serologic group have been residents of the county over 5 years and 76 percent over 10 years. There seems to be no evidence that there has been an influx of outsiders into the county, and this is perhaps the reason for the low prevalence of syphilis.

Marital Status.—Figure 1 shows the relationship of the marital status to the serologic reactions. The greatest prevalence of syphilis as shown by positive serologic tests is in the separated group, 46 percent in the female and 36.2 percent in the male. This is to be expected as

promiscuity on the part of one of the married partners is the usual cause for separation.

Relationship of Occupation to Serologic Status.—The relationship of occupation to serologic findings is shown in tabular form in table 3. The percentage of positive serologic reactions corresponds closely to that obtained in other smaller surveys done in the State. Domestic servants as well as food handlers are required to have blood tests. Other surveys have shown from 25 to 33 percent positive reactions in this combined group. Our percentage was 25.4. Prenatal examinations in the State have been showing from 15 to 20 percent positive reactions so that our figure of 17.2 percent for housewives corresponds closely. It should be explained that the group headed "self-employed," which shows the greatest percentage of positives includes mostly persons operating a small business or shop, such as a shoe repair shop, a boarding house, a laundry, a grocery store.

Previous Medical History.—We found a history of symptoms as well as presence of symptoms suggestive of syphilis

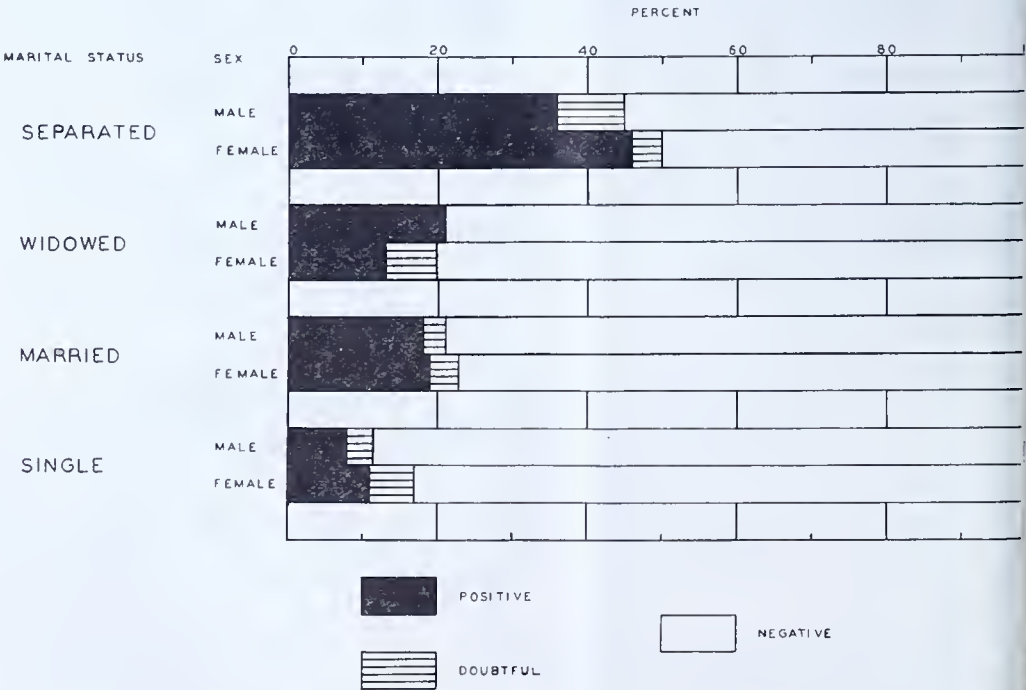


FIGURE 1.—Percentage of positive and doubtful serologic tests for syphilis by sex and marital status.

fection more frequently in patients with positive serologic reactions for syphilis than in those with negative reactions.

Effect of Syphilis Upon Pregnancies.—Stokes (6) mentions the increased conception rate usually found among syphilitic women. Our study does not agree with this as will be seen in table 4. This table shows that in almost all age groups the conception rate is lower in the syphilitic than in the nonsyphilitic woman. The average number of pregnancies in the syphilitic group above 20 years of age was 3.5, while in the nonsyphilitic was 4.4. In women who had conceived we found that the syphilitic woman had

had an average of 4.3 and the nonsyphilitic woman an average of 5.2 pregnancies. In this same age group 81 percent of the syphilitic and 85 percent of the nonsyphilitic women had conceived, probably showing a higher sterility rate in the syphilitic woman. We also found that 7.8 percent of the seropositive and 10.5 percent of the seronegative women in the child-bearing age were pregnant at the time of our survey. Table 5 shows a slightly lower percentage of positive and doubtful reactions among pregnant women than among women who were not pregnant.

TABLE 3.—Occupational status of individuals surveyed, with serologic and malaria findings

Occupation	Malaria		Serologic results						Total	
			Positive		Doubtful		Negative			
	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
farm owner.....	3	1.3	40	17.0	8	3.4	187	79.6	235	100.0
farm tenant.....	9	2.9	46	14.9	16	5.2	246	79.9	308	100.0
school child.....	63	4.6	61	4.4	93	6.8	1,222	88.8	1,376	100.0
school child.....	9	2.1	14	3.2	10	2.3	412	94.5	436	100.0
laborer.....	8	2.8	49	17.1	10	3.5	227	79.4	286	100.0
housewife.....	6	1.6	65	17.2	16	4.2	298	78.6	379	100.0
domestics and food-handlers.....	2	1.6	32	25.4	5	4.0	89	70.6	126	100.0
professional.....	1	5.0	1	5.0	1	5.0	18	90.0	20	100.0
self-employed.....		.0	8	29.6	2	7.4	17	63.0	27	100.0
none.....		.0	5	9.8	2	3.9	44	86.3	51	100.0
Total.....	101	3.1	321	9.9	163	5.0	2,760	85.1	3,244	100.0

TABLE 4.—Pregnancies in females by age groups and serologic status

Age group	Serologic status	Total females		Have had pregnancies		Total number of pregnancies	Average pregnancies for females who have been pregnant
		Number	Percent	Number	Percent		
All ages.....	Positive.....	176	100.0	127	72.2	519	4.1
	Doubtful.....	66	100.0	34	51.5	159	4.7
	Negative.....	1,043	100.0	535	51.3	2,635	4.9
19 years.....	Positive.....	30	100.0	9	30.0	11	1.2
	Doubtful.....	30	100.0	2	6.7	4	2.0
	Negative.....	460	100.0	42	9.1	56	1.3
29 years.....	Positive.....	56	100.0	39	69.6	118	3.0
	Doubtful.....	10	100.0	9	90.0	28	3.1
	Negative.....	211	100.0	161	76.3	490	3.0
39 years.....	Positive.....	45	100.0	39	86.7	158	4.1
	Doubtful.....	9	100.0	8	88.9	25	3.1
	Negative.....	137	100.0	119	86.9	664	5.6
49 years.....	Positive.....	23	100.0	19	82.6	124	6.5
	Doubtful.....	7	100.0	7	100.0	42	6.0
	Negative.....	85	100.0	79	92.9	553	7.0
50 years and over.....	Positive.....	22	100.0	21	95.4	108	5.1
	Doubtful.....	10	100.0	8	80.0	60	7.5
	Negative.....	150	100.0	134	89.3	872	6.5

TABLE 5.—*Females in child-bearing age 15-45: Number who were pregnant at time of survey and relationship to serologic findings*

Serologic status	Females in child-bearing age		Pregnant at time of survey		Not pregnant at time of survey	
	Number	Percent	Number	Percent	Number	Percent
Positive.....	128	16.7	10	13.2	118	17.7
Doubtful.....	37	4.8	3	3.9	34	4.9
Negative.....	600	78.5	63	82.9	537	77.3
TOTAL.....	765	100.0	76	100.0	689	100.0

Serologic and Treatment History.—All persons tested were questioned regarding previous serologic tests and amount of treatment received. Table 6 shows the results of our questions. It will be seen that only 18.7 percent of the persons whom we found to be positive gave a history of a previously positive blood test. In our doubtful cases 4.8 percent had previously been positive, and 1.4 percent of the negative cases had been positive. Apparently the physicians in this area have been somewhat suspicious of syphilis as 39.3 percent of our positive cases had had a prior blood test while only 15.5 percent of the negative cases had had one. Presumably about 15 percent of our positive cases have become positive since the physician tested them, or they were misinformed of the result of the test. Only 4 cases of syphilis were reported to the State board of health from Onslow County in 1939.

The treatment history of persons surveyed clearly shows the inadequacy of treatment received in an area where no public clinics are available. We found that 81.3 percent of the positive cases had had no treatment. Among women who had been pregnant we found that only 8.4 percent of those with a positive serologic reaction had had previous anti-syphilitic treatment, while in the doubtful group 3.0 percent and in the negative group 2.9 percent had had treatment.

RESULTS OF MALARIA SURVEY ²

Prevalence.—In a total of 3,244 persons tested we were able to find malaria protozoa in the blood of 101 (3.1 per-

cent). We were able to do a second, third, or fourth test in 92 of these 10 patients with malaria protozoa. Plasmodium falciparum (estivo-autumnal) was found in 93.1 percent, and Plasmodium vivax (benign tertian) in 6.9 percent of those infected. Parasites were again found in 38 of the 92 persons who were reexamined.

Malaria History and Treatment Received.—Malaria has been present in Onslow County for a great many years. As early as 1884, the reports to the State board of health show that it was a very common disease, especially in the fall months. Fifty-four deaths from malaria were reported from this county during the past 19 years. Malaria was made reportable in 1937 and since the only 5 cases of malaria have been reported although there have been deaths.

We questioned all persons regarding malaria history and found that 1,069 (33.7 percent) gave a history of having had malaria. The results of our questionnaire are shown in table 7. We note that 45.8 percent of all persons who have had malaria claim to have been treated by a physician. Considering that the same proportion of all cases received treatment from a physician in the year prior to our survey, we can estimate that approximately 200 patients were thus treated. Reporting of malaria by physicians is therefore negligible.

² In this paper the presence of malaria parasites in the blood is considered as evidence that the person has malaria, although it is realized that in many cases no symptoms of the disease are present.

TABLE 6.—*Previous blood tests and treatment-history of all cases surveyed with present serologic findings*

Previous blood tests, year in which they were performed, and history of treatment	Present serologic findings					
	Positive		Doubtful		Negative	
	Number	Percent	Number	Percent	Number	Percent
PREVIOUS BLOOD TESTS						
1st year—Positive.....	16	5.0	2	1.2	7	0.3
1-5 years—Positive.....	32	10.0	3	1.8	21	.8
Over 5 years—Positive.....	12	3.7	3	1.8	8	.3
1st year—Negative.....	3	.9	2	1.2	31	1.1
1-5 years—Negative.....	37	11.5	5	3.1	235	8.5
Over 5 years—Negative.....	10	3.1	2	1.2	39	1.4
Unknown.....	16	5.0	5	3.1	94	3.4
Total.....	195	60.8	141	86.5	2,325	84.2
TOTAL,	321	100.0	163	100.0	2,760	100.0
TREATMENT						
1st year.....	16	5.0	3	1.8	5	.2
1-5 years.....	31	9.7	4	2.5	22	.8
Over 5 years.....	13	4.0	3	1.8	11	.4
Total.....	261	81.3	153	93.9	2,722	98.6
TOTAL,	321	100.0	163	100.0	2,760	100.0
AMOUNT OF TREATMENT						
Under 5—Neo. no heavy metal.....	12	3.7	2	1.2	12	.4
5-10—Neo. no heavy metal.....	24	7.5	6	3.7	14	.5
10-20—Neo. no heavy metal.....	10	3.1	2	1.2	4	.2
Over 20—Neo. no heavy metal.....	2	.6	—	—	—	—
Under 5—Neo. under 5 heavy metal.....	4	1.3	—	—	3	.1
5-10—Neo. 6-10 heavy metal.....	4	1.3	—	—	2	.1
10-20—Neo. 11-20 heavy metal.....	2	.6	—	—	—	—
Over 20—Neo. above 20 heavy metal.....	1	.3	—	—	—	—
Neo. under 10 heavy metal.....	1	.3	—	—	3	.1
Total.....	261	81.3	153	93.9	2,722	98.6
TOTAL,	321	100.0	163	100.0	2,760	100.0

Age, Sex Distribution of Malaria.—Approximately 77 percent of all cases of malaria that we found occurred in the age group below 20. There was the usual slightly higher prevalence rate in the male than in the female—3.4 percent and 2.8 percent, respectively (table 1).

Occupational Distribution of Malaria.—Table 3 shows the occupational status of all patients who had malaria. Of the total number, 72 percent were preschool and school children, and approximately 18 percent of the total were outside workers, laborers, and farm tenants.

TABLE 7.—*Malaria history of population surveyed showing time-period in which malaria was acquired and type of treatment*

	Number	Percent
Individuals questioned.....	3,244	100.0
History of malaria.....	2,150	66.3
History of malaria.....	1,094	33.7
History of malaria in past year.....	423	38.7
History of malaria 1-5 years ago.....	256	23.4
History of malaria over 5 years ago.....	415	37.9
TOTAL.....	1,094	100.0
Treatment received:		
Physicians.....	501	45.8
Home treatment, herbs, etc.....	501	45.8
Patent medicines.....	40	3.7
Quinine.....	11	1.0
None.....	41	3.7
TOTAL.....	1,094	100.0

TABLE 8.—*Serologic results, malaria and history of malaria by district*

District Number	Malaria						Serologic results						Total	
	Positive malaria		History of malaria		Neither malaria nor history of malaria		Positive		Doubtful		Negative			
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
1-----		0.0	43	16.1	224	83.9	22	8.2	14	5.3	231	86.5	267	100
2-----	3	.6	132	26.8	357	72.6	56	11.4	23	4.7	413	83.9	492	100
3-----		.0	41	30.1	95	69.9	9	6.6	6	4.4	121	89.0	136	100
4-----	3	5.1	18	30.5	38	64.4	3	5.1	4	6.8	52	88.1	59	100
5-----		.0	51	31.3	112	68.7	18	11.0	5	3.0	140	86.0	163	100
6-----	15	5.2	152	52.2	124	42.6	36	12.4	25	8.6	230	79.0	291	100
7-----	4	2.7	50	34.3	92	63.0	18	12.3	8	5.5	120	82.2	146	100
8-----	1	1.1	17	17.9	77	81.0		.0	1	1.0	94	99.0	95	100
9-----	32	12.5	136	53.1	88	34.4	25	9.8	15	5.8	216	84.4	256	100
10-----	5	3.1	70	42.9	88	54.0	10	6.1	5	3.1	148	90.8	163	100
11-----		.0	17	25.8	49	74.2	15	22.7	3	4.6	48	72.7	66	100
12-----	3	1.8	70	41.7	95	56.5	8	4.8	11	6.5	149	88.7	168	100
13-----	1	.6	58	33.3	115	66.1	20	11.5	8	4.6	146	83.9	174	100
14-----		.0	17	28.3	43	71.7	6	10.0	5	8.3	49	81.7	60	100
15-----	4	2.3	60	34.1	112	63.6	18	10.2	6	3.4	152	86.4	176	100
16-----		.0	31	15.6	168	84.4	6	3.0	1	.5	192	96.5	199	100
17-----	8	3.7	70	32.1	140	64.2	30	13.8	12	5.5	176	80.7	218	100
18-----	22	19.1	61	53.1	32	27.8	21	18.2	11	9.6	83	72.2	115	100
Total-----	101	3.1	1,094	33.7	2,049	63.2	321	9.9	163	5.0	2,760	85.1	3,244	100

Geographic Distribution of Malaria.—

The distribution of cases in the districts of the county is shown in table 8. Districts number 9 and 18 have the highest prevalence rate, 12.5 and 19.1 percent respectively. These districts are swampy in many places and are near stagnant fresh water. Farther inland the elevation is greater; farther seaward the water becomes brackish, especially at high tide. Neither of these conditions offers a suitable breeding place for the anopheline mosquito.

The same districts, 9 and 18, which showed the highest prevalence rate of malaria also had a history of the highest malaria rate (table 8). In these districts 53 percent of all people surveyed gave a history of having had malaria. District number 6 had a history of high malaria incidence, 52.2 percent, but a relatively low prevalence, 5.2 percent. This district, which includes the town of Jacksonville, has recently had considerable drainage work done by WPA labor—an example of a work project that has shown very valuable results.

In malaria as in syphilis we can find no evidence to show that the disease is being brought into the county by out-

siders, 57.4 percent of the malaria cases having resided in the county over years and 86.1 percent over 5 years.

Seasonal Occurrence of Malaria.—The greatest number as well as the highest percentage of positive malaria smears were obtained in October. This taken into consideration initial tests on The highest percentage of positive findings was observed on repeat examinations in March. This shows that a number of patients who had positive tests earlier in the season were still infected at the time the tests on them were repeated. Both of these findings quite well coincide with the usual distribution of estivo-autumnal malaria in this latitude.

Change in Serologic Reaction.—It has been fairly well established by various investigators that false positive blood serologic reactions for syphilis are very common in malaria. Kitchen and workers (7) have shown that apparently nonsyphilitic persons who are given therapeutic malaria will at some time or other have a false positive serologic reaction in the course of the malarial infection. The findings in our survey are shown in table 9. We can divide our false se-

gic reactions on the first test into 32.4 percent false positives, 32.4 percent false doubtfuls, and 3.8 percent false negatives. This is in a group who would be considered out-patients and the type whom the private physician would be called upon to treat either at home or in his office.

In individuals without demonstrable malaria parasites in the blood we found also an appreciable number of false serologic reactions. There were 13 percent false positive and 11.8 percent false doubtful reactions. The North Carolina State Laboratory of Hygiene has participated in the national serologic sur-

veys and its work is considered satisfactory. We must conclude, therefore, that many of the individuals tested in this malarious region, who did not have demonstrable parasites in the blood, did have enough reagin to cause false positive and doubtful serologic reactions. There seems to be no doubt of the value of repeat serologic tests in such an area. Examination of a thick blood smear for malaria parasites in conjunction with the serologic test seems advisable although the absence of malaria parasites should not be considered conclusive evidence that a patient has syphilis if the blood serologic reaction is positive.

TABLE 9.—Changes in serologic results between first and second tests in malaria and nonmalaria patients

INDIVIDUALS WITH TWO SEROLOGIC TESTS	Without malaria		With malaria	
	Number	Percent	Number	Percent
First test positive or doubtful	421	100.0	37	100.0
No change in reaction	316	75.1	13	35.1
Remained positive	280	66.5	11	29.7
Remained doubtful	36	8.6	2	5.4
Change in reaction	105	24.9	24	64.8
Positive to doubtful	9	2.1	2	5.4
Positive to negative	46	10.9	10	27.0
Doubtful to negative	41	9.7	11	29.7
Doubtful to positive	9	2.1	1	2.7
First test negative			53	100.0
No change in reaction			51	96.2
Remained negative			51	96.2
Change in reaction			2	3.8
Negative to positive			1	1.9
Negative to doubtful			1	1.9

TABLE 10.—Serologic results of first and second tests in malaria positive cases with relative number of malaria parasites found

Number of malaria parasites in test		Serologic results							
		Positive		Doubtful		Negative		Total	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent
First test	Many	7	26.9	6	40.0	19	31.7	32	31.7
	Few	5	19.2	3	20.0	14	23.3	22	21.8
	Rare	9	34.6	4	26.7	27	45.0	40	29.6
	None	5	19.2	2	13.3	0	0	7	6.9
	Total	26	100.0	15	100.0	60	100.0	101	100.0
Second test	Many	3	23.1	0	0	2	2.8	5	5.6
	Few	2	15.4	1	20.0	7	9.7	10	11.1
	Rare	4	30.8	0	0	24	33.3	28	31.1
	None	4	30.8	4	80.0	39	54.2	47	52.2
	Total	13	100.0	5	100.0	72	100.0	90	100.0

Effect of Malaria on Final Serologic Classification.—Table 2 shows the percentage of positive reactions in the malaria group to be 10.9 compared with 7.5 in the group of those persons who did not have malaria. The difference in the doubtful rate is more marked, being 23.8 percent in people with malaria, 5.6 percent in those with a history of malaria, and 3.8 percent in those who had never had malaria.

Relationship of Number of Parasites to Serologic Reaction.—We could find no definite relationship between the number of parasites found in the smears and the serologic reaction in the initial test. In the repeat test the negative serologic group alone was consistent, 2.8 percent showed many parasites, 9.7 percent few, 33.3 percent rare, and 54.2 percent none (table 10).

Effect of History of Malaria on Final Serologic Classification.—In table 2 is shown a definitely higher percentage of positive serologic reactions in those persons with a history of malaria, namely 14.2, than in those without this history, 7.5. Our findings also showed that 48.6 percent of persons with positive, 37.4 percent with doubtful, and 31.8 percent with negative serologic reactions have had malaria; 12.8 percent of persons with positive, 19.0 percent with doubtful, and 12.7 percent with negative serologic reactions had had malaria during the year prior to our survey. In figure 2 we have combined the positive and doubtful serologic reactions in order to show graphically the effect of past history of malaria upon serologic findings. In those persons who have had malaria there is a gradual increase in percentage of positive and doubtful reactions until the age of 60. In persons who have not had malaria there is the usual type of curve wherein the middle age groups contain the highest percentage of positive reactions with a decreasing percentage in both the younger and older age groups. Until approximately the twenty-fifth year, the percentage of positive and doubtful reactions is greater in those persons who have had malaria.

Between the ages of 25 and 45 there is an increased percentage of positive and doubtful reactions in those persons who have not had malaria. After 45 the group who have had malaria again show increased percentages of positive and doubtful reactions. Kitchen and coworkers (7) have shown that therapeutic malaria will cause false positive serologic reactions for as long as 66 days after the parasite disappears from the blood. Perhaps natural malaria will form enough antigen to cause false reactions for much longer periods of time. Therapeutic malaria has been considered of value in preventing certain forms of neurosyphilis. Perhaps natural malaria may be of value in preventing syphilis; there is a noticeable increase in percentage of positive and doubtful reactions in the group who have not had malaria during the middle third of life when exposure to syphilis is greatest. More studies along this line seem to be indicated before any conclusions can be drawn.

SUMMARY

1. A serologic test for syphilis and thick-smear microscopic examination for malaria parasites have been made on over 80 percent of the Negro population of Onslow County, North Carolina.
2. Examinations were made of 3,244 persons, and 9.9 percent gave positive serologic reactions.
3. Examinations for malaria showed the malaria parasite to be predominantly *Plasmodium falciparum* (estivo autumnal).
4. Malaria parasites were found in 3.8 percent of persons tested.
5. Data are presented showing the age, sex, marital, occupational, and geographic distribution of the persons with positive serologic reactions.
6. Graphs and charts are presented to show the effect of syphilis upon the outcome of pregnancies.
7. The inadequacy of serologic testing, treatment of syphilitic persons, and the reporting of syphilis and malaria cases in this area is pointed out.

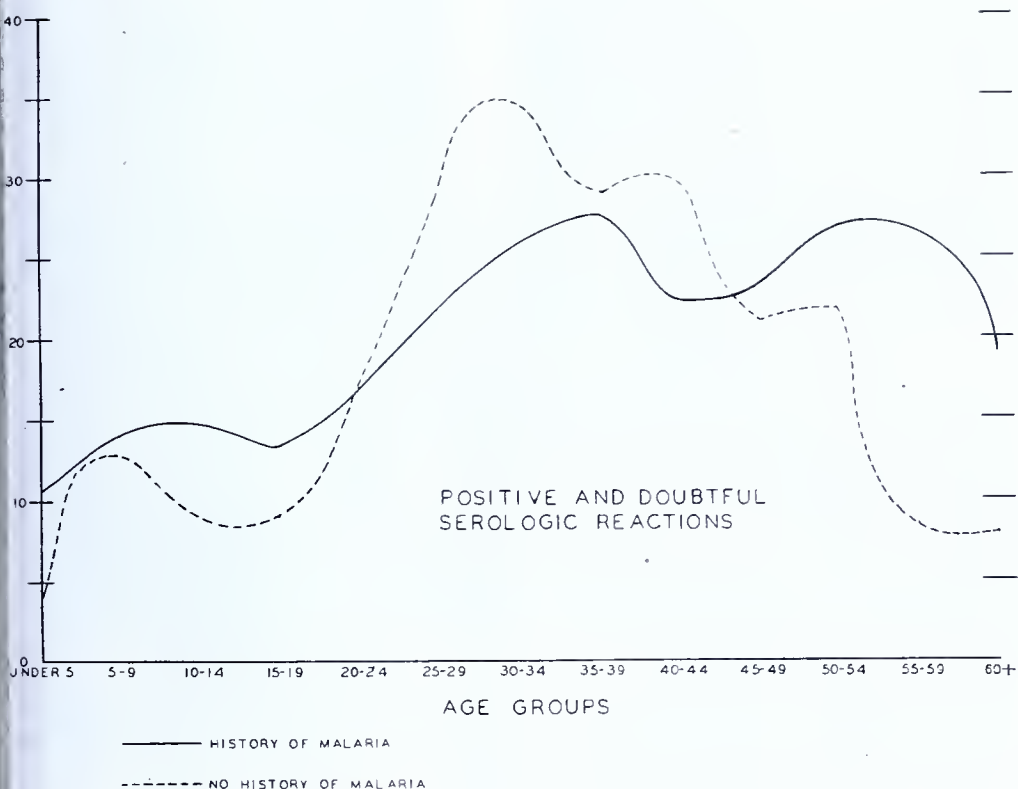


FIGURE 2.—Effect of history of malaria upon positive and doubtful serologic reactions by age groups.

8. The age, sex, geographic, occupational, and seasonal distribution of malaria cases are shown.

9. When malaria parasites were present in the blood, disagreement between first and second serologic tests occurred in 64.8 percent of the cases in which the first test showed a positive or doubtful reaction. Disagreement in cases where no parasites could be found occurred in 24.9 percent.

10. The error of diagnosing syphilis on the basis of one serologic test is shown.

11. Data are presented which show an increase in the percentage of positive and doubtful serologic tests in persons with a history of malaria over those who do not have such a history.

12. Additional data collected in the survey are presented.

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Spontaneous Healing and Progression in Untreated Venereal Lymphogranuloma

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POSITIVE skin reactions with Frei antigen in patients who do not present symptoms of venereal lymphogranuloma are of frequent occurrence. It is conceivable that a previous infection accounts for such a result. Case histories frequently fail to support this explanation, and the theory of asymptomatic infection has been advanced to explain positive skin tests of the described kind. Judging from some observations, it might be questionable whether asymptomatic infection would be able regularly to produce strong reactivity of the skin. The occasional presence of scars rather suggests the probability that in such cases, and in some others, lesions had been present but had healed without treatment. It is understandable that the patient who did not care much about, and who was not much bothered by, his infection is likely to retain only a hazy recollection of it.

The number of patients with venereal lymphogranuloma who have had no treatment is surprisingly large. In 1939, 93 patients were admitted to the clinic with venereal lymphogranuloma, 65 of them with recent and 27 with chronic infection, mostly rectal strictures. Thirty of the newly infected patients (46.2 percent) did not return to the clinic for treatment after the buboes had been aspirated or the skin tests performed. Twenty patients (30.8 percent) discontinued treatment as soon as some improvement was perceptible. Only 15 patients remained regular in their attendance until dismissed. On the other hand only 3 patients out of the 27 with old and resistant lesions disappeared be-

fore receiving treatment, and 2 of them did so because they left the city. Evidently the patients who became delinquent in the first stages were not much bothered by the disease. The conclusion that spontaneous healing occurs promptly is confirmed by observations on patients who remained under control but whose treatment was delayed. The same observation has been reported by several authors. This, of course, refers only to the more acute symptoms.

In order to determine final results in untreated patients, a long period of observation is essential. We reexamined 41 untreated patients. In 16 of them the lesions showed evidence of healing and in 25 the lesions remained unchanged. These figures do not represent the true percentage of spontaneous healing since the unhealed patients return because of their symptoms, whereas the ones with healed lesions were called or were examined when encountered by chance in another clinic and thus probably form a relatively small part of the spontaneously healed group. On the other hand, patients with the least tendency to spontaneous improvement are apt to remain under treatment and therefore are not found among the untreated cases. The important point, however, is the observation that, in a considerable number of patients with venereal lymphogranuloma, healing of lesions occurs

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thout treatment. A short survey of the cases is presented.

CASE 1. L. S., Negro woman, 22 years old, was seen on August 15, 1938, with a slightly fluctuant bubo of 2 weeks' duration. The test for chancroid was negative and the Frei test, 4 plus. Three weeks later the bubo was subsiding. The patient was pregnant, and the bubo was not treated. On January 2, 1939, the patient presented herself with lesions on the fourchette which were diagnosed as *granuloma inguinale*. The previously observed bubo had disappeared. The test for chancroid was negative, the Frei test, 4 plus.

CASE 2. Negro male, 19 years old, was seen on January 24, 1939, with a fluctuant bubo in the right groin of 4 weeks' duration. No penile lesion was present. The test for chancroid was 1 plus; the Frei test, 4 plus; the Wassermann reaction, negative. On November 27, 1939, small glands were palpable in the right groin. The test for chancroid was 1 plus, the Frei test, 4 plus.

CASE 3. Negro woman, 26 years old, presented herself on April 12, 1937, with enlarged, firm, matted glands in both groins. The test for chancroid was 1 plus; the Frei test, 4 plus; the Wassermann reaction, negative. On January 2, 1939, no signs of inguinal venereal lymphogranuloma were found. The test for chancroid was negative, the Frei test, 4 plus. The Wassermann reaction had become positive (4 plus). On November 2, 1939, the findings were unchanged.

CASE 4. Negro male, 18 years old, presented a fluctuant bubo of the left groin on November 17, 1937. The test for chancroid was negative; the Frei test, 4 plus; the Wassermann reaction, negative. On January 12, 1938, the Wassermann reaction was 4 plus. The bubo had completely disappeared. On November 2, 1939, multiple chancroids were observed. Smears from these lesions were positive for Ducrey's bacillus. The left inguinal glands were slightly tender. The test for chancroid and the Frei test were both 4 plus.

CASE 5. Negro male, 22 years old, was seen on November 18, 1935, with a bubo of the left groin. No skin tests were performed at that time, but the clinical description and the results of skin tests performed later confirmed the diagnosis of venereal lymphogranuloma. On January 8, 1940, the patient was seen again. At this time he had dark field-positive primary syphilis. The bubo had disappeared. The test for chancroid was negative, the Frei test, 4 plus.

CASE 6. Negro woman, 37 years old, was seen on January 8, 1937, with a slightly fluctuant bubo in the left groin. The test for chancroid was 1 plus, the Frei test, 4 plus. January 30, 1940, the patient had salpingitis but no sign of venereal lymphogranuloma. The test for chancroid was 1 plus, the Frei test, 4 plus.

CASE 7. Negro woman, 17 years old, was seen on August 25, 1938, with enlarged, firm, matted glands in the left groin. The test for chancroid was negative; the Frei test, 4 plus; the Wassermann reaction, negative. Three weeks later the buboes were subsiding. The reaction to the skin tests was unchanged. On August 1, 1939, the patient was seen with primary syphilis of the vulva. The test for chancroid was negative; the Frei test, 4 plus; the Wassermann reaction, 4 plus. On January 12, 1940, after anti-syphilitic treatment, there were no lesions and no rectal stricture. The inguinal glands were somewhat enlarged. The reaction to the skin tests remained the same as before.

CASE 8. Negro woman, 39 years old, was seen on April 16, 1936, with buboes in both groins. The test for chancroid was negative, the Frei test, 4 plus. Five days later the buboes had opened spontaneously. On August 9, 1938, the patient returned because of gonorrheal involvement of the left Bartholin gland. There was no inguinal swelling, a small scar in the left groin being the only abnormal finding.

CASE 9. Negro woman, 22 years old, was seen on January 14, 1936, with swelling in the left groin of 2 weeks

duration. On February 11, 1936, the glands, which had shown temporary improvement, were again slightly fluctuant. The test for chancroid was negative, the Frei test, 4 plus. On April 17, 1936, another recurrence following temporary improvement was noted. Between January 5, 1937 and November 29, 1939, the patient was frequently examined because of chronic pelvic inflammation. No sign of venereal lymphogranuloma was found. The skin tests were unchanged.

CASE 10. Negro woman, 17 years old, was seen December 15, 1937, with suppurating and draining bubo, following primary syphilis. The test for chancroid was 1 plus; the Frei test, 4 plus; the Wassermann and Kahn tests, negative. On May 5, 1939, Wassermann and Kahn tests had become 4 plus; the test for chancroid was 1 plus and the Frei test, 4 plus. At this time there was only a small round scar in the left groin.

CASE 11. Negro male, 21 years old, was seen July 12, 1937, with swelling of the penis and scrotum and fluctuant bilateral buboes. Aspiration of the right bubo supplied pus for an effective Frei antigen. The test for chancroid was negative, the Frei test, 4 plus. The same results were obtained on repetition of the tests. On October 23, 1939, firm, bean-sized lymph nodes were palpable in the right groin. A small, smooth, slightly depressed scar was visible in the left groin. There was no lesion on the penis. The Frei test was 4 plus, the test for chancroid, 4 plus. An indefinite history of a penile lesion in the interval between observations was given.

CASE 12. Negro male, 27 years old, was seen on May 27, 1936. Small superficial ulcers had appeared on the penis 3 weeks before; a bubo in the right groin had been draining for the past 2 weeks. The test for chancroid was negative, the Frei test, positive. On May 29, 1940, a small irregular right inguinal scar remained; there was no scar on the penis. The test for chancroid was negative, the Frei test, 4 plus.

CASE 13. Negro male, 22 years old, was seen April 3, 1936, with fluctuant

bubo of the left groin and phimosis. Dorsal slit revealed an uncharacteristic erosion, possibly caused by gonorrheal discharge. The test for chancroid was negative, the Frei test, 4 plus. On November 16, 1937, he had no complaint; the skin tests were unchanged. On May 20, 1940, the patient complained of constipation. There was no sign of rectal stricture. A small scar was visible in the left groin, a small depressed scar on the prepuce. The test for chancroid was negative, the Frei test, positive (slight necrosis).

CASE 14. Negro male, 31 years old, was seen on November 10, 1936, with fluctuant bubo of the left groin. The test for chancroid was negative, the Frei test, 4 plus. On May 12, 1939, several punched-out ulcers had developed on the penis. The inguinal glands were not enlarged. On May 24, 1939, the ulceration was spreading. Smears revealed fusospirochetosis. Both chancroid and Frei tests were 4 plus. The glands in the right groin began to enlarge; a small scar was visible in the left groin.

CASE 15. Negro woman, 28 years old, was seen June 12, 1937, with a slightly fluctuant bubo of the left groin. The test for chancroid was 2 plus; the Frei test, 4 plus. On January 30, 1940, she had acute pelvic inflammation. Scars were visible in the groin. The test for chancroid was 1 plus, the Frei test, 4 plus.

CASE 16. Negro male, 31 years old, presented ulceration of the penis on December 11, 1936. The ulceration was superficial, small, moderately indurated, and not sensitive. The dark-field examination was negative; the test for chancroid, negative; the Frei test, 4 plus. On December 14, 1936, the Frei test had become positive (4 plus). The left inguinal glands were swollen, matted together, hard, moderately sensitive. Swelling in the right groin was noticeable. Two weeks later the left bubo discharged enormous amounts of pus. No treatment, except dressings, was given. On June 26, 1940 (patient had gonorrhea and positive Wassermann

at time), the left inguinal glands were somewhat enlarged, matted, painless. No scars were visible. The test for chancroid was negative, the Frei test, plus.

All these cases healed without treatment. In cases 1 to 7 and 15, not even a scar was visible. In cases 9 to 14, and possibly 8, scars remained as evidence of previous disease. In case 16 the glands still retained the characteristic qualities of venereal lymphogranuloma years after the infection. It is important to emphasize that this group includes only patients with bubo, all but three of whom (3, 5, 7) presented definite suppuration. Some of the patients had ulcers as well as buboes. Ulcers or elephantiasis with little or no involvement of the glands were not found in this series. Apparently the absence of a bubo diminishes the tendency to spontaneous healing. (This statement does not refer to superficial early ulcers which may be transient.)

The unhealed cases also supply observations which emphasize the unique position of the bubo in the disease picture. In contradistinction to the healed cases, this group of 25 includes only 11 patients (7 male, 4 female) who had suffered from unilateral or bilateral bubo, while 14 (3 male, 11 female) had presented ulcers or early elephantiasis when first seen.

The type of subsequent manifestation was significant. Following bubo, three male patients presented chronic lymphadenitis and elephantiasis. In six patients (4 male, 2 female) the bubo had reappeared after apparent healing. One woman presented the urethral syndrome. (Here the preceding bubo was not definitely caused by venereal lymphogranuloma.). Only one woman who previously had been seen with bubo had anal tabs; perhaps these were precursors of rectal stricture. Following ulcers and early elephantiasis, the anorectal syndrome developed in 5 women; the other patients (3 male, 6 female) presented ulcerative lesions, elephantiasis,

or the urethral syndrome on reexamination.

These findings indicate that buboes not only have a natural tendency to heal spontaneously but that they also influence the character of possible sequelae. They are followed by extensive elephantiasis and especially by rectal stricture less frequently than other lesions. Where late manifestations developed following untreated bubo, the latter, as a rule, had not healed completely and was involved in the process. On the other hand, invasion of the inguinal lymph nodes did not occur in the late stage of the disease, even if the area drained by these nodes was involved, e. g., the clitoris.¹

The most interesting finding was the rare occurrence of rectal stricture after bubo. A history of bubo is seldom obtained in patients with rectal stricture. Torpin, Greenblatt, Pund and Sanderson obtained only three histories of bubo among 22 patients, and 15 of their patients gave no history of infection prior to the development of rectal stricture. In a series of 42 women with rectal strictures, 30 gave no history of previous manifestations of venereal lymphogranuloma; 9 presented either a history or findings of ulcerations or elephantiasis; only 3 patients gave a history of bubo, 1 of whom had positive reactions to both chancroid and Frei tests.

This finding cannot be accounted for by the alleged rarity of bubo in women. The same investigators observed buboes in 29 out of 97 consecutive cases of venereal lymphogranuloma in women and obtained a positive history in 4 other cases. Buboes are not an altogether infrequent finding in women. They are seen in a high percentage of women with venereal lymphogranuloma who have acute lesions. In a series of 46 such cases, we observed 14 ulcers with

¹ Independently of this series, a patient with rectal stricture was observed in whom a bubo developed with the characteristic signs of venereal lymphogranuloma and whose test for chancroid was negative.

little or no involvement of the inguinal glands and 32 buboes. The rare occurrence of rectal stricture following bubo, therefore, requires explanation. A certain antagonism between bubo and rectal stricture is acknowledged by most authors. Cole, as well as Barthels and Biberstein, believes the particular lymph supply of the female to be responsible for the rarity of inguinal and the frequency of rectal localization in women. Since a history of bubo is rare only in cases of rectal stricture but not in connection with other lesions in women, the almost complete mutual exclusion of both types of manifestation cannot be fully explained by the anatomical condition, the more so because elephantiasis and genital tabs often involve both the inguinal and the iliac lymphatic areas.

The observations on untreated cases might offer a point in solving the problem. The favorable prognosis following bubo is apparently related to its spontaneous healing. The bubo seems in some way to affect the fate of the virus outside of the lymph nodes, for example, the healing of a genital ulcer as soon as the bubo develops. Ulcerations without concomitant bubo, except the superficial ones, are usually resistant, and their chance of spontaneous healing is slight, as shown in this investigation. From a wealth of experience in other diseases, it may be concluded that the acute involvement of the bubo, which promotes its spontaneous healing, incidentally accounts for its influence upon an otherwise chronic disease, while the absence of early marked inflammation favors the development of late sequelae. It is evident from the findings that early inflammation other than bubo has a similar though less powerful effect. Most of the rectal strictures develop without any early preceding manifestations. A few details about the unhealed cases may illustrate certain features of venereal lymphogranuloma.

In one woman a urethral syndrome and elephantiasis developed within 9 months following a small ulcer at the urethral orifice. In another, 9 years was

required for the development of marked elephantiasis. The same is true in rectal stricture. Such differences in spontaneous development deserve consideration in estimating the value of therapeutic methods. Men are less subject to chronic progressive venereal lymphogranuloma than women. If our explanation of the antagonism between bubo and rectal stricture is correct, it might also be applied here: The anatomical conditions in contradistinction to those in women, favor involvement of the inguinal glands, which in turn cuts short the entire infection. The types of late lesions that were seen in the male are significant. Of two untreated patients with penile ulcer and without bubo with a negative test for chancroid, a 4-plus Frei test, and a negative Wassermann reaction, elephantiasis of the scrotum and penis developed in one within 2 years; a progressive, destructive, bleeding ulcer developed in the other within 9 months. In 5 of 6 patients, whom late manifestations had developed following bubo, the latter, as stated above, had not undergone spontaneous healing but was involved in the morbid process—another evidence for the connection that exists between absence of sequelae and the spontaneous healing of bubo.

In several cases the bubo had subsided completely but had again undergone suppuration after a long interval. Recurrence was described by Trousseau (1866, quoted by Cole). We do not know whether reinfection could account for some of these observations. At least in the following case, exposure was unlikely. A. C., a (?) 65-year-old colored man, was seen December 18, 1937, with fluctuant bubo in the left groin, indurated bubo in the right groin, and ulcer of the prepuce. The test for chancroid was 1 plus; the Frei test, 4 plus; the Wassermann reaction, 4 plus. In November 1939 he was seen again. He stated that he had been well all the time until 2 weeks previously. There was a bluish, fluctuant, painless bubo in the right groin. Scars were visible

the prepuce and in the left groin. The tests were unchanged. The patient died having been exposed for the past year. He became delinquent as before, and again the bubo healed spontaneously, at least temporarily.

SUMMARY

Venereal lymphogranuloma may heal spontaneously, the tendency to heal varying with the different types of manifestation of this disease. Buboes possess far the best chances, especially after suppuration. Established elephantiasis and rectal stricture have no tendency to spontaneous healing. In recent ulcerations, spontaneous healing occurs only rarely except for superficial primary lesions or those accompanied by bubo. Scars may or may not be present to indicate the healed lesion. Some positive skin tests in healthy persons who have no signs or history of venereal lymphogranuloma may be explained by the quick and spontaneous healing of the past infection.

A small number of patients experienced recurrent suppuration after a long interval. Chronic elephantiasis with lymphadenitis may develop in patients with bubo. Rectal strictures were only exceptionally seen to develop in untreated patients who had presented a bubo. Correspondingly, a history of bubo was frequently elicited in cases of rectal stricture. As buboes frequently occur in women, the mutual exclusion between inguinal and rectal involvement cannot be fully explained by anatomical conditions or lymphatic drainage. The development of a bubo apparently plays an active part in the prevention of late sequelae. A genital lesion of venereal lymphogranuloma may start to heal as soon as the bubo develops, whereas, in the absence of bubo, the ulcerations are persistent and if untreated are often followed by late manifestations. Late manifestations following bubo are more likely to occur if the bubo has not healed spontaneously. The possibility of spontaneous healing and its various as-

pects must be kept in mind in evaluating therapeutic measures.

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New Feature in Venereal Disease Information

Monthly Appraisal of the Sulfonamides

ON THE back page of this issue of *VENEREAL DISEASE INFORMATION*, there appears the first report to be published on "Rapid Appraisal of Sulfonamide Drugs in the Treatment of Gonorrhea in the Male." Rapid appraisal was placed in operation in January 1941 by the American Neisserian Medical Society and the United States Public Health Service to provide interested clinicians with up-to-date information on the comparative effectiveness of the succession of sulfonamide drugs which have been introduced in the treatment of gonorrhea. The appraisal is conducted by pooling the current case reports of a group of clinics for analysis of the results of treatment on a cumulative basis. Hitherto, rapid appraisal reports in the form of tables have been made directly to the interested clinics and to the venereal disease control officers of the United States Public Health Service. Because of the need for wider dissemination of information on the comparative value of the sulfonamides in general use, however, it was believed that a graphic report published each month in *VENEREAL DISEASE INFORMATION* would be of value to many clinics and physicians. Meanwhile, direct reports to the participating clinicians and public health officers on drugs introduced for clinical experimentation will be continued. These reports will also be sent to the pharmaceutical laboratory manufacturing the drug and to others who request this information from the Division of Venereal Diseases, United States Public Health Service, Washington, D. C.

DIAGNOSIS

The skin eruption and false-positive Wassermann in infectious mononucleosis (glandular fever). Joseph F. Sadowski, Jr. *Internat. Clin.*, Philadelphia, 1: 239-255, 1941.

The fact that a skin eruption and a temporary false positive Wassermann reaction may both be present, either singly or together, in infectious mononucleosis is not well known. During the past 14 years, 7 percent of the 54 cases of infectious mononucleosis seen in the New Haven Hospital exhibited a skin eruption during the course of the disease, and 13 percent of 45 cases upon which repeated serologic tests for syphilis were carried out showed positive reactions. Ordinarily the false positive reaction appears during the second week of disease and rarely during the latter part of the first week. It usually reverts to negative within 2

weeks, although it has been seen as long as 3 months. The eruption involves the trunk and upper arms, occasionally the face and forearms. The rash appears most frequently from the fourth to the tenth day, although it may appear as late as the twentieth. Itching is mild or absent.

That infectious mononucleosis may be mistaken for syphilis and antisyphilitic therapy actually instituted has been recorded. A generalized lymphadenopathy, maculopapular eruption, positive serologic tests for syphilis, and even fever or splenomegaly, may closely resemble secondary syphilis. It may be differentiated from syphilis by the presence of an unusual cervical adenopathy, absence of rash on hands or feet, positive blood picture of infectious mononucleosis and a positive Paul-Bunnell test. Demonstration of *Treponema pallidum* in the secondary lesions by dark-field examination is, of course, diagnostic of syphilis. In the absence of both a positive dark-field examination and a definitely positive Paul-Bunne

st, the diagnosis may rest on observation of the clinical and serologic course, less the characteristic mononucleosis with abnormal young lymphocytes is present.

Four cases are discussed which had been followed in the New Haven Hospital. The skin eruption in 2 instances assumed a macular appearance and in the other 2 it was of a maculopapular and morbilliform nature. The Kahn reaction became positive in all 4 cases; the Wassermann became positive with the cholesterolized antigen in 2 cases and positive with the alcoholic antigen in 1 case. In 41 cases of mononucleosis without skin eruption a positive serum reaction occurred in only 2 instances. It would seem, therefore, that the positive serum reaction is actually more apt to occur in those cases in which a rash is manifest than in the other cases.

Routine Kahn blood reactions. Supplementary report of 20,000 tests made on Naval recruits with observations on the relationship of cowpox vaccination to the false positive test. G. E. Thomas and R. W. Garrity. U. S. Nav. M. Bull., Washington, 39: 272-276, Apr. 1941.

This report supplements one published in January 1941 which covered 10,000 tests, and the two reports include 20,000 tests made on recruits entering the Naval Training Station, San Diego, between July 1939 and January 1941. All tests were run by the same technicians. In the entire series of 20,000 there were 7 (0.365 percent) positive initial Kahn tests, of which 32 (0.16 percent) proved to be false positives and 41 (0.205 percent) were persistently positive. Of the 41 positive cases, 10 were definitely believed to have acquired syphilis, 3 to have congenital syphilis; 20 probably had the disease and 8 were exceedingly doubtful. Of this group of positive cases 6 percent had had promiscuous relations with prostitutes, 28 percent had had few sexual contacts, and 7 percent denied sexual intercourse.

The findings suggest a definite relationship between cowpox vaccination and

the false positive test. In the first 10,000 tests the blood was taken after vaccination; in this group there were 26 false positives. In the second 10,000 the blood was taken before vaccination, and there were only 6 false positives. One particular case in the second group is cited. This recruit had a negative Kahn reaction on arrival and 3 weeks after vaccination a strong positive which persisted for 3 weeks, since which time it has remained negative.

No relationship between antityphoid inoculation and the false positive Kahn test could be found. Several recruits from the Southern Gulf States developed clinical malaria after their arrival, and all of these had positive Kahn tests at some time during their treatment.

The tests which were found to be falsely positive became negative within a period of 4 weeks.

TREATMENT

Sulfathiazole treatment of gonococcal infections in ambulatory patients.

Luca E. Celentano and Robert M. Lewis. Connecticut M. J., Hartford, 5: 344-346, 394, May 1941.

In the New Haven Municipal Venereal Disease Clinic, sulfathiazole has been used since June 1940 for both male and female patients with gonorrhea as follows: Grams 2 (grains 30) daily for 12 days only, the daily dose being divided into 4 doses. Patients are warned that no other drug is to be taken during the time sulfathiazole is taken. Sexual excitement and alcohol are prohibited. No other restrictions are ordered. Local treatment is not given except occasional warm water douches for women. Patients are instructed to stop taking the tablets if they have fever, vomiting, diarrhea, severe headache, or body rash. All patients visit the clinic 3 times a week while under treatment and thereafter once a week for 2 months and, in the case of women, once every 2 weeks for

2 more months. For proof of cure an observation period of 4 months is considered necessary for women and for men an 8 weeks' observation after they have become symptom free.

Sulfathiazole has been used for 35 men and 25 women. All the women and 33 of the 35 men were rapidly cured. Sulfanilamide had been given previously with no success to 18 of the men. Under sulfathiazole therapy, 10 of these 18 men became symptomless in 5 to 7 days, 3 in 4 days, 1 in 3 days, and 4 in 2 days. Of the 17 who had sulfathiazole only, 13 were symptom free in 5 to 7 days. None of the patients had any type of untoward reaction, whereas 5 of the 18 who had had sulfanilamide previously had reported toxic reactions to that drug. There were no complications.

A special method of taking smears and cultures in the female is described. A bivalve speculum is inserted and the cervix is squeezed between the lips of the speculum. The swab is inserted well into the cervical os and rolled rather than rubbed over the slide.

Treatment of gonorrheal diseases of the eye with sulfanilamide. Three years' clinical experience. Carroll R. Mullen. *Arch. Ophth.*, Chicago, 25: 655-658, Apr. 1941.

At the Philadelphia General Hospital, where more than 80 patients with gonorrheal infection of the eye have been treated during the past 3 years, 42 patients were treated with sulfanilamide administered both locally and internally.

In this series of 42 patients there were 14 infants with ophthalmia neonatorum of gonorrheal origin and 28 older patients who had gonorrheal infection of the conjunctiva and cornea. All of the 14 infants were discharged without corneal involvement. Of the 28 patients with gonorrheal ophthalmia, 5 had corneal complications when discharged.

Sulfanilamide was given internally in doses of 1 to 2 grains (0.06 to 0.12 gm.) per pound of body weight, but never more than a total of 100 grains (6 gm.) for the first 24 hours of hospitalization.

Irrigations of the involved eye using 2 percent boric acid solution followed free instillations of a 0.8-percent solution of sulfanilamide were carried out at 15 minute intervals day and night.

Mullen believes that in cases of gonorrheal ophthalmia the internal treatment with sulfanilamide could be omitted in favor of almost continuous irrigation (with that drug) of the diseased cul-de-sac, with equally good results. He does not intend to conduct experiments to prove this point, however, when so many authorities have advocated the importance of internal use of the drug.

Studies of the blood were performed in all cases before administering the drug and also during treatment. There were no toxic effects from its use. When there was a lowering of the erythrocyte count or the hemoglobin level, the drug was discontinued or the dosage was decreased.

After the first 24 hours of treatment the internal dosage of sulfanilamide was decreased to 0.025 to 0.03 gm. for each pound of body weight.

The use of atropine sulfate solution in strengths varying from 0.25 to 1.0 percent (according to the age of the patient), iced wet applications for 15 minutes every hour, and a Bullar shield when only one eye was involved completed the therapeutic measures. Instillation of atropine sulfate was continued until the patient was discharged.

No patient was considered ready for discharge until negative smears had been reported on three successive days and sequelae or complications had developed which needed further treatment.

In several cases negative smears were obtained during the day that treatment was started. In other cases of early involvement 3 to 6 days of treatment were required before the smears became negative.

Complications which were present at the time of admission or which developed during the course of treatment included (a) rupture of the cornea with prolapse of the iris on admission, (b) posterior synechiae (possibly from an o

itis), (c) corneal ulcer present on admission in two cases, (d) leukoma present on admission in one case, (e) superficial erosion of the cornea in one case (this cleared up during treatment), and (f) hazy corneas on admission in two cases (these all cleared up during treatment). One patient died 3 days after admission, on the day after the last negative smear was obtained.

The length of time which elapsed between the onset of infection and the beginning of treatment varied from 2 days to 2½ months. The patient whose treatment was delayed for 2½ months was admitted with a steamy cornea and discharged with a clear cornea.

Red eruptions. Report of an unusual condition due to sulfanilamide. M. H. Goodman and Robert D. Arthur. *Arch. Dermat. & Syph.*, Chicago, 43: 692-697, Apr. 1941.

The patient, a robust 18-year-old Negro with an acute gonorrheal urethritis, insisted under the direction of a physician to take 10 grains of sulfanilamide on July 7. His dosage was reduced gradually to 30 grains daily until the third week of August, when the urethral discharge had stopped. At this time because of an itching eruption on the skin the drug was discontinued. During the following week the eruption almost subsided, but because of a reappearance of the discharge the patient was again given 20 grains of sulfanilamide on August 31. The following morning there was a recrudescence of the original lesions with an increase in their size. The largest lesion and the first one to appear was on the anterior surface of the upper part of the right thigh. It was a round, palm-sized macular area with a uniformly deep violaceous red with a finely scalloped border. Although the color was not completely blanched out on pressure the minimal infiltration and edema suggested a superficial involvement of the skin. There were other smaller lesions scattered over the right side of the body, on the left side of the chest, the back, and the pubic area. With the discontinuance of sulfanilamide the eruption

began to disappear. On September 7, sulfapyridine therapy was begun because of relapsing urethritis. In spite of continued administration the cutaneous lesions had faded out by September 22. The urethral discharge had ceased on September 10.

On September 25 the patient was given a test dose of 10 grains of sulfanilamide, and 10 hours later there was a recurrence of the lesions at the original sites, all of the patches showing moderate increase in diameter. Patch tests with moistened sulfanilamide powder were performed on the patient's skin to determine whether there was evidence of allergic hypersensitivity, but they were all negative in result. Intradermal tests were also negative. A segment for biopsy was removed, and two features of special interest were observed in the microscopic section. The epidermis showed absence of melanin pigment and clouding of the nucleus and cytoplasm of the prickle cells; the cells of the basal layer were hydropic. The inflammatory process in the cutis was strictly limited to the blood vessels and their immediate environs in the papillary and subpapillary layers. The blood vessels showed decided swelling of their walls with rounding out and constriction of the lumens. They were surrounded by a zone of edema in which there was an intense infiltrate composed chiefly of lymphocytes, interspersed, especially at the margin, by a great number of large mononuclear cells laden with deep brownish melanin pigment. The authors believe that these features are characteristic, if not pathognomonic, of the fixed exanthem. They feel also that the peculiar arrangement in this case of the typical lesion with outlying rings of papules possibly signifies that the hypersensitivity resides in the nerves or blood vessels.

Our experience in the treatment of the proctitis of Nicolas-Favre's Disease. A. Midana. *Dermatologica*, Basel, 82: 339-349, No. 5/6, 1940.

The author presents the results of his experience extending over a period of 10

years in the treatment of approximately 40 patients with proctitis due to venereal lymphogranuloma. He obtained the best results with sulfonamide therapy but emphasizes two conditions necessary for successful treatment: (1) Intermittent treatment over a long period of time which requires the greatest patience and perserverance on the part of both patient and physician, and (2) the local application of sulfonamides in addition to peroral therapy.

The scheme of treatment consists of the peroral administration over a period of 20 days of 2 gm. sulfanilamide daily, or, if this produces gastric disturbance, 1 gm. per os and either 5 cc. of a 20-percent solution intravenously or 3 cc. of a 33-percent solution intramuscularly. After a rest period of 10 to 15 days, a second course is given. Occasionally a third course is given following the same rest period. After an interval of 2 to 3 months another series of courses of treatment is begun. Locally 100 cc. of a 1-percent solution of a sulfonamide are injected into the rectum once or twice daily with the aid of a rubber balloon. The last injection is preferably given at bedtime, following a preliminary cleansing of the rectum with boiled water.

Sulfonamide therapy may be alternated by treatment with antimony preparations and iodides. The author was not impressed with the results of roentgen-ray, diathermy, or antigen therapy. Surgical treatment can be applied only to certain cases.

Remarks on spirochetal vaccine (Hilgermann). K. Zieler. *Dermat. Wchnshr.*, Leipzig, 110: 373, May 11, 1940.

In regard to K. Bruder's article on spirochetal vaccine (*Dermat. Wchnshr.* No. 9, vol. 110) the author points out that earlier reports as well as Bruder's own observations have shown that the action of Hilgermann's vaccine is a non-specific one. He also questions whether Hilgermann's spirochetes are *Spirochaetae pallidae*. He points out that Hilgermann's spirochetes were at one

time investigated by the Frankfurt Institute for Chemotherapy but that the results of the study were never published and states that a report of his work at the present time would solve many questions and would save a lot of study which otherwise will be necessary.

The treatment of ophthalmia neonatorum. J. S. du Toit. *South African M. J.*, Capetown, 15: 103, Mar. 2, 1941.

The incidence of ophthalmia neonatorum in Capetown is still fairly high, even in institutions where adequate preventive measures are supposed to be adopted. The reason for this is that in many cases the drugs used as prophylactics are old and useless, and the law requiring use of prophylactics is probably not enforced very strictly.

This disease is the cause of about 5 percent of the blindness in the institutions and about 50 percent of blindness in children. It is responsible for more blindness than any other disease.

Since the beginning of 1938, different methods of local treatment have been adopted in the eye department of the Groot Skuur Hospital, and the relative values of these drugs have been determined. There was very little difference in the results of treatment and in the duration of stay in the hospital with the use of such drugs as mercurochrome, acriflavine, and the various silver preparations, and irrigations. During the period from the beginning of 1938 to April 1939, 32 patients were given sul treatment. In 10 of these cases, corneal ulcers developed, and serious loss of vision resulted in most of them.

Since May 1939, sulfapyridine has been given in addition to local treatment. The local treatment has usually consisted of irrigations with potassium permanganate, boric acid, or saline solutions. Sulfapyridine was administered in doses of $\frac{1}{7}$ grain per pound of body weight, given three times daily powdered, placed on the tongue, and washed down with the food. It was

that the dosage might be too small in some cases, but it was considered desirable to avoid the possibility of producing toxic symptoms and so necessitate discontinuing the drug.

Thirty-two patients were treated by means of chemotherapy, and, although initial treatment was found to be practically unnecessary, the eyes seemed to improve more satisfactorily when irrigations were used to keep the conjunctival sac free from excessive secretion. Immediate clinical results were good in many cases, and the purulent discharge was diminished. Edema of the lids and conjunctival chemosis rapidly subsided. Only a few of the patients showed even slight symptoms of intolerance.

When sulfapyridine was given, the average stay of patients in the hospital was reduced to 6 days. Although 5 patients were admitted with corneal involvement, the infection rapidly cleared without the loss of the sight of a single eye. None of the patients had corneal involvement after treatment with sulfapyridine was begun.

rapidly increasing dyspnea, which became so severe that a tracheotomy was considered. Laryngoscopic examination showed a paralysis of the recurrent nerve of the right vocal cord but no edema or lesions of the larynx. Her symptoms of dyspnea gradually disappeared. On examination of the lungs many sonorous and sibilant râles were heard over both lung fields; at the right base there was slight suppression of both sonorous and vesicular breath sounds. A roentgen-ray examination of the chest at this time showed dilatation of the bronchi, particularly those on the right, the hilar shadows extending toward the diaphragm giving the appearance on the right side (where this finding was most marked) of a beginning pleural effusion. The Wassermann reaction was strongly positive. On being questioned in regard to a syphilitic infection at this time the patient stated that she had given birth to a dead child at the age of 18 years. Just before this pregnancy she had had an eruption on the body, the Wassermann reaction had been positive, and she had received a series of intravenous injections. She had not completed her treatment, and a Wassermann test 4 years after she had taken treatment had been negative. Two of her brothers had died of tuberculosis.

Antisyphilitic treatment with cyanide of mercury was given on May 24. On May 26 there were definite signs of pleural effusion at the base of the right lung. Cloudy fluid containing staphylococci but no tubercle bacilli was aspirated. On May 27 the patient again became dyspneic and cyanotic; the larynx was not found to be involved, and therefore a tracheotomy was not done. The patient died on this day.

Tertiary syphilis of the trachea, though a rare condition, is, according to these authors, not as infrequent as commonly believed. It is often confused with tuberculosis and carcinoma. Its occurrence in a 30-year-old woman is here reported.

Since July 1939, at which time she had been 20 years old and a cough, she had been losing weight and a productive cough had developed. In February 1940 she had to go to bed, but at this time the roentgen-ray examination of the chest was negative, and no tubercle bacilli could be found in the sputum. In May she had

An autopsy was performed. Marked pleural effusion on the right side was found. The right lung, especially the lower lobe, was dense and congested. Except for absence of effusion the changes in the left lung were the same. Section showed the two bronchi of the two bases to be enlarged and filled with greenish pus. There was definite cylind-

PATHOLOGY

Some considerations on tertiary syphilis of the trachea. E. Sergeant, A. Bergerson, M. and Mlle. Oehmichen. *Presse Méd.*, Paris, 48: 1065-1067, Dec. 25-28, 1940.

drical bronchiectasis. Just above the bifurcation there was marked constriction associated with thickening of the wall of the trachea. A large lymph node was seen just beneath the bifurcation of the trachea. All other organs were essentially normal.

Histologic examination of the lymph node above mentioned showed caseofibrous degeneration, areas of lymphocytic infiltration, and giant cells. The trachea in the area of constriction showed a thickened, granular, mucosal surface and small gummata containing giant cells and surrounded by areas of leukocytic infiltration. The alveoli of the affected lung areas were filled with fibrin, and polymorphonuclear and mononuclear leukocytes. Tubercle bacilli could not be demonstrated in this material.

An anatomic-pathologic report of a rare observation in visceral syphilis: Macrogumma of the heart. D. Mariotti. *Gior. ital. di dermat. e sif.*, Milano, 81: 1043-1061, Dec. 1940.

Two cases of multiple, large heart gummata are described. In the first, in which the patient died following the development of marked signs of decompensation, the right ventricle showed extensive replacement of heart muscle by syphilitic granulomatous tissue and by scar tissue. In the second case there were practically no symptoms preceding death from pulmonary embolism. In this case extensive gumma formation was found in the walls of both ventricles. Histologic study showed that the granulomatous process had extended to involve the endocardium, as the result of which thrombi were formed on the endocardial surface. The pulmonary embolism which resulted in the death of the patient was the result of detachment of one of these thrombi.

The author concludes that the varied symptom-complex of syphilitic diffuse gummatous involvement of the heart makes clinical diagnosis of this condition practically impossible. Anatomically he differentiates 3 types of heart gumma: (1) Gummata involving the myocardium of the outer walls; (2) gummata involv-

ing the myocardium of the septa; gummata which develop in the direct of the heart cavity and lead to endocardial involvement.

LABORATORY RESEARCH

Duration of infectivity of *Treponema pallidum* in citrated blood stored under conditions obtaining in blood banks. Thomas B. Turner and Thomas H. Discker. *Bull. Johns Hopkins Hosp.*, Baltimore, 68: 269-279, March 1941.

The transfer of whole blood from one person to another by the immediate direct method carries with it the potential risk of transmitting syphilitic infection. A recent report lists 138 cases of indubitable transfusion syphilis, and among these there were 20 cases in which the routine serologic examination of the donor's blood did not disclose the presence of the infection. Since many hospitals now maintain blood banks, the authors have conducted the present study in order to obtain information on the probable limits of safety in using such blood even though it was taken from a syphilitic donor. Virulent *Treponema pallidum* were added to citrated blood from both human beings and rabbits, and the infectivity of the mixture for rabbits determined after various periods of refrigeration. Blood from syphilitic rabbits known to be in an infectious stage was likewise tested.

The authors feel the experiments indicated that, under conditions obtaining in blood banks, syphilis treponemes probably undergo progressive deterioration during the storage period. Virulent *Treponema pallidum* added to citrated whole human blood failed to give rise to infection in normal rabbits after storage periods of 48 hours or longer. When added to citrated whole rabbit blood and similarly stored, virulent treponemes were infectious for normal rabbits after

hours' storage but not after 72 hours longer. In a similar experiment by Schick (to be published) infection was maintained after a storage period of 72 hours. Nevertheless, the results of the above studies are in substantial agreement, and indicate that the infectivity of syphilitic treponemes in citrated blood rarely persists for longer than 3 days at refrigerator temperature. It is probable that blood stored for 4 days or longer does not transmit the disease.

In a few instances normal rabbits were infected when transfused with naturally infected rabbit blood which had been stored for 48, 72, or 96 hours.

On the ability of Wassermann reagins to permeate into the cerebrospinal fluid and the constancy of specific reactions in the cerebrospinal fluid. H. Saker. *Deutsche Ztschr. f. Nervenheilk.*, Berlin, 152: 29-36, Feb. 1941.

In 5 patients with seropositive latent syphilitic infection but with negative spinal fluid, the effect of irritative (sterile) meningitis on the spinal fluid reaction was studied. In 3 of these cases autopsies were performed, and no evidence of syphilitic change in the central nervous system was obtained. The spinal fluid Wassermann reaction remained negative in spite of marked meningeal reactions, e. g., marked increase in cell count, albumin, and globulin. In one of these cases the spinal fluid Wassermann was slightly positive on 2 occasions but in this case the spinal fluid had been contaminated with blood.

That the presence of sterile meningitis does not modify a strongly positive Wassermann reaction of the spinal fluid was shown in 3 cases, in which from 3 to 6 examinations of the spinal fluid were made. This finding does not lend support to the view of Strobel and others that the strength of the Wassermann reaction is dependent on the protein content and that an absolute or relative increase in the globulins increases the strength of the Wassermann reaction whereas an increase in albumins decreases it.

In a series of 10 seronegative, non-syphilitic patients it was shown that a sterile meningitis, regardless of degree of severity, does not produce nonspecific positive Wassermann reactions of the spinal fluid. This also has been the author's observation in purulent meningitides.

The author points out that the flocculation test applied to the spinal fluid is not as reliable an indicator of syphilis as the Wassermann test. It is almost always positive in compression spinal fluid and not rarely also in the presence of nonspecific meningitides and brain tumors. These nonspecific positive flocculation reactions occur without any regularity. The flocculation test may be positive in the presence of relatively low protein values and may be negative with high protein values. It is therefore not dependable as an auxiliary test in doubtful cases of neurosyphilis.

In vitro studies were made to determine the effect of various bacteria (streptococci, staphylococci, and pneumococci), and roentgen-ray and ultraviolet irradiation on the Wassermann and flocculation reactions of positive cerebrospinal fluid obtained from patients with general paresis. The influence of bacteria and roentgen-ray irradiation was found to produce no change in the reactions, but ultraviolet irradiation changed strongly positive Wassermann and flocculation reactions of the spinal fluid to weakly positive or negative reactions. The author therefore cautions laboratory workers against exposing spinal fluid to sunlight.

The effect of sodium dehydrocholate on arsphenamine hypoglycemia. L. Bertellotti. *Gior. ital. de dermat. e sif.*, Milano, 81: 1071-1089, Dec. 1940.

The author first determined the effect of intravenous injection of various doses of a 20-percent solution of sodium dehydrocholate on the blood sugar level of 10 rabbits. It was found that a subtoxic dose resulted in hyperglycemia. Hyperglycemia was also produced in man with therapeutic doses (3 to 5 to

10 cc.) and occurred as early as 2 minutes after injection. The normal level was reestablished after 2 to 3 hours.

Next, the effect of intravenous injection of neoarsphenamine on the blood sugar level was determined. In 4 rabbits injected intravenously with a dose of 0.02 to 0.03 gm. per kg. of body weight a constant fall in the blood sugar level could be observed. In man the injection of therapeutic doses resulted in a fall in the blood sugar level as early as 2 minutes after injection. There was a return to normal blood sugar values in 2 to 3 hours.

The effect of the injection of a mixture of sodium dehydrocholate and neoarsphenamine was then studied. It was found that sodium dehydrocholate neutralized the hypoglycemic effect of neoarsphenamine. The dose of sodium dehydrocholate did not seem to make much difference, although 3 cc. apparently suffices to prevent the hypoglycemic effect of 0.6 gm. of neoarsphenamine. The effect produced was the same whether the two substances were mixed before injection or were injected one immediately after the other.

Study of sulfonamide chemotherapy and reinfection in experimental Nicolas-Favre's disease. P. Cerutti. *Gior. ital. di dermat. e sif.*, Milano, 81: 1031-1042, Dec. 1940.

The effect of sulfonamide therapy (streptosil De Angeli) on white mice which had been experimentally inoculated intracerebrally with the virus of venereal lymphogranuloma was studied. It was found that this treatment decreased the severity of the resulting meningo-encephalitis, 6 out of 10 of the animals still being alive 45 days after the inoculation. Streptosil, however, was found to have no effect on the virus in vitro. That the virus of venereal lymphogranuloma is still present in the inoculated animals which have been treated with sulfonamide was demonstrated by the fact that brain emulsions made from these animals retained their pathogenicity for other healthy animals. Reinoculation of the surviving animal

(whether spontaneously or as a result of sulfonamide treatment) is said to be followed by an attenuated form of meningo-encephalitis; the animal almost never dies. This was found to be true whether the strain used for the reinoculation is the same as that used for the first inoculation or whether it is a different strain.

The author formulates the hypothesis that the sulfonamides do not act on the virus of venereal lymphogranuloma itself but that they modify the terrain, probably by the formation of an unknown substance in the animal organism in a way which makes it unsuitable for the growth of the pathogenic agent.

Blood sugar and liver glycogen. I. A study of single doses of sulfanilamide, sodium sulfapyridine and sodium sulfathiazole. Esther M. Greisheimer, Robert Hafkesbring and Hulda Magalhães. *M. Times*, New York, 69: 170-171, Apr. 1941.

The effect of single doses of sulfanilamide, sodium sulfapyridine, and sodium sulfathiazole upon blood sugar and liver glycogen was studied on fasting rats which received glucose after a 15-hour fast. The dose of sulfanilamide was 1.8 cc. of 1 percent solution per 100 grams of rat; this was given by the intraperitoneal route. The doses of sodium sulfapyridine and sodium sulfathiazole were 1 cc. of 10 percent, 1 cc. of 9 percent, and 1 cc. of 7.5 percent solutions per 100 grams of rat.

The study showed that the general level of the blood sugar and the functions of glycogen formation and storage are not interfered with by sulfanilamide in a single dose of the size used. In contrast to this, the administration of sodium sulfapyridine is followed by an increase in blood sugar and by alteration in both glycogen formation and storage; this held for the 3 doses used. The greater the dose the more pronounced the effects. The administration of sodium sulfathiazole is followed by a marked increase in blood sugar; in this respect it resembles sodium sulfapyridine. However,

ually toxic doses, it has little effect on liver glycogen. When given in larger doses (10 percent), in which there is about 50 percent mortality, it leads to a decrease in liver glycogen. The authors conclude from this that in usually toxic doses, sodium sulfapyridine is more harmful to the liver than sodium sulfathiazole.

Concentration of free sulfanilamide, sulfapyridine, and sulfathiazole in material drained from human biliary tract. Roger S. Hubbard and Winfield L. Butsch. *Proc. Soc. Exper. Biol. & Med.*, Utica, 46: 484-487, Mar. 1941.

Two grams of sulfanilamide, sulfapyridine, and sulfathiazole were ingested in successive experiments by 4 patients from whom bile was draining through tubes inserted in the bile duct after operations upon the biliary tract. Intervals of 3 or 4 days separated the experiments upon each subject. Specimens of bile were collected for 4 successive 4-hour periods in each experiment. Samples of urine were collected simultaneously with the bile specimens after the drug had been given, and a sample of blood was drawn at the midpoint of each of the three 4-hour periods.

The results upon the blood and bile of different subjects were qualitatively similar. The actual relationships between the concentrations in blood and bile were sufficiently alike in the different patients to justify presenting an average of the figures. There was a lack of quantitative relationship between the amounts of the drugs present in the blood and urine, and this suggests (particularly in the experiments upon sulfanilamide) that the rate of excretion of these substances is relatively constant when the urine volume is constant. The excretion of the drugs into the bile shows marked qualitative differences, which was present in each of the individual experiments. Considerable amounts of sulfanilamide were present in the bile. These paralleled approximately the concentrations in the blood, but the value of the ratio increased during the latter part of the experiments.

The concentration of sulfathiazole in the bile was very low throughout the periods of study and increased rather than diminished in spite of the drop in the concentration in the blood. The results with sulfapyridine were more irregular than were those obtained with the other two drugs, and perhaps are associated with the effect of the known irregularities in the absorption of this compound upon the blood concentration.

The results with sulfathiazole are difficult to interpret. It is possible that this relative failure of passage into the liver is an expression of a general relatively low diffusibility of this compound. The authors point out one result of the difference in concentration of sulfanilamide and sulfathiazole in the bile. When relatively large amounts of a readily absorbed substance enter the bile and are returned to the intestine the time during which the compound remains in the body is prolonged. Excretion by the liver, therefore, will tend, at least slightly, to prolong the period during which sulfanilamide remains in the body as compared with the time sulfathiazole remains in the body.

The "sulfanilamide death time" in vitro of 106 strains of the gonococcus. Charles M. Carpenter and Harold F. Wingate. *J. Bact.*, Baltimore, 41: 473-478, Apr. 1941.

In this study an attempt has been made to correlate the "sulfanilamide death time" of each strain of the gonococcus with the period of its cultivation, with its thermal death time, and with the amount of sulfanilamide necessary to effect a clinical "cure" of the patient from whom the strain was obtained. The effect of sulfanilamide treatment of the patient on the subsequent resistance of the organism to the drug has also been observed.

In this study 106 strains of the gonococcus were employed 64 of which were recovered from males, 33 from adult females, and 9 from children with vulvovaginitis. The generations ranged from the 3rd to the 400th. Eighteen of the

strains were isolated from patients after treatment with sulfanilamide.

The sulfanilamide death time of the 106 strains in a 1:10,000 concentration of the drug ranged from 8 hours to more than 48 hours. Approximately $\frac{1}{2}$ of the cultures became nonviable after exposure to the drug for from 12 to 24 hours. Recently isolated strains were less resistant to the drug than were strains that had been grown on an artificial medium for a long period of time. The mean death time of the youngest group, represented by 52 strains which had been cultivated for from 1 to 20 generations, was 17.7 hours; of the oldest group, represented by 14 strains cultivated for from 101 to 400 generations, it was 33.7 hours; and of the intermediate group, represented by 31 strains cultivated for from 21 to 100 generations, it was 28 hours.

There was little difference in the sulfanilamide death time of strains derived from patients who had been treated with sulfanilamide and those from untreated individuals. There was no correlation between the death time of a strain of the organism and the amount of treatment with sulfanilamide required to accomplish a clinical "cure."

In a study of 31 strains on which the thermal death time at 41.5° C. had been determined, as well as the sulfanilamide death time in a concentration of 1:10,000, no direct correlation of the bactericidal action of the two agents could be discovered.

Observations on the origins of the 106 cultures offered no evidence that the source of the strain affected the sulfanilamide death time.

PUBLIC HEALTH ADMINISTRATION

The evaluation of premarital legislation.

W. M. Sheppe. J. A. M. A., Chicago, 116: 2006, May 3, 1941.

Requirements regarding the restriction of marriage of persons found to be in-

fected with syphilis vary greatly in the 26 States which have some type of legislation covering this point. In general, the issuance of a license is based on the result of physical examination, laboratory tests, or in some instances the medical certification of freedom from venereal disease by a registered physician. The medical profession has not been unanimous in its sanction of the legislative efforts.

Data on the actual number of cases of syphilis detected by premarital requirements is as yet fragmentary. Sheppe has corrected and brought up to date the figures published by the 13 States for which statistics are thought to be reliable there have been 677,832 persons examined. Of these, 9,017 had positive reactions, a percentage of 1.3. This incidence of syphilis in the premarital group is fairly uniform throughout the country. It is apparently lower than the incidence of cases in the general population, but this difference may be apparent rather than real, as persons who know that they have syphilis probably do not apply for examination. A high proportion of the persons who were found to have syphilis were unaware of their infection.

The figures for West Virginia show a higher incidence (2.4 percent) than in any other State for which figures are available. This is of interest, for West Virginia is the first southern State to present any statistics of this type. Most of the premarital blood examinations are performed in private laboratories in West Virginia, the State laboratory having carried out 3.1 percent of the positive examinations. The premarital law in West Virginia has proved acceptable to a large majority of the medical profession and the general public.

Sheppe feels that the favorable results accruing from the enforcement of premarital legislation far outweigh the theoretical objections which have been advanced.

tes on 1940—A national defense year. Walter Clarke. J. Social Hyg., New York, 27: 163-165, Mar. 1941.

At the end of 1940 the entire resources of the American Social Hygiene Association were being devoted, directly and indirectly, to national defense work. Current publications deal mainly with defense problems. Educational activities point out the relation of sound sex instruction to the prevention of syphilis and gonorrhea. Publicity stresses defense activities. Medical activities deal with syphilis and gonorrhea in relation to the Army, the Navy, and industrial workers. A new film, In Defense of the Nation, was completed for release in April 1941.

The most intensive defense effort has occurred in the field of legal and protective measures, the principal services being detailed field studies of existing conditions in regard to commercialized prostitution in the vicinity of military and industrial concentration areas. Such surveys were made in 129 cities in 23 States and the District of Columbia, and in 46 areas near Army, Navy, and industrial establishments. A. S. H. A., public health and medical consultants are continuously available to employers.

Officers and staff have given time to the encouragement of those positive preventive measures—provision of wholesome recreation and morale-maintenance activities—which are of great importance to the prevention of venereal disease. Substitutes for the brothels and honky-tonks must be provided by the morale-maintenance agencies if the job of cleaning up vicious prostitution situations is to be done.

While concentrating on meeting emergency needs, long-range objectives have been kept in view, and all work has been planned and carried out with these aims in view.

How the Army protects soldiers from syphilis and gonorrhea. Arthur Parker Hitchens. J. Social Hyg., New York, 27: 103-112, Mar. 1941.

The Medical Corps of the United States Army has the duty of selecting men with qualifications highly specialized for the defense of the Nation and then of maintaining and improving those qualities. It is, therefore, incumbent upon the Army administrators to know and deal with the causes of noneffectiveness and permanent disability of the armed forces. Achievement of this purpose includes not only physical fitness, but also the maintenance of morale.

The punitive measures adopted in the early history of the United States frequently caused a young soldier, upon finding himself infected, to seek the advice of a patent medicine vendor. At present the infected soldier loses pay while he is away from duty because of his disease, but he suffers court-martial only if he fails to report for treatment. The responsible Army officer has effective cooperation of local police and extracantonment health officials. Any person known to be a source of infection will be kept in confinement until made noninfectious by treatment.

The Army is well aware of the importance and potential values that wholesome recreational and educational opportunities have for soldiers, thereby preventing some men from visiting prostitutes from whom practically all venereal infections are acquired. No gain is made by assuming a vindictive, disparaging attitude toward an infected man. The job is to treat his illness when he is infected and to use efforts to change the conditions which are likely to increase the probability of his becoming infected.

Hitchens emphasizes the need for building a firm and unequivocal opposition to legalized prostitution on the part of the public. The less accessible brothels are, the less profitable they are to their owners, and the less likely they are to flourish.

Protecting industry from venereal diseases. Warren F. Draper. *J. Social Hyg.*, New York, 27: 98-102, Mar. 1941.

Prevention of venereal disease is a contribution to physical fitness, and physical fitness is the underlying contribution that can be made to the national defense program. The Surgeon General of the United States Army showed that last year 239,000 days were lost in the Army through absence from duty because of venereal disease. A similar situation evidently exists in industry, judging from the syphilis found among the young men called for selective service. There is little or no information regarding the loss of time by workers as a result of venereal disease. However, blood tests of workers in large industrial centers have shown that from 20 to 40 in every 1,000 workers are infected with syphilis. With defense industries doubling and redoubling their production, the employer and employee must unite in a fight against the sabotage of syphilis and gonorrhea.

The United States Public Health Service has formulated a tentative plan for combating venereal disease in a community of industrial workers. One essential is that routine blood tests should be performed at the time a man is employed and at regular intervals thereafter. A positive blood test presents no cause for denying employment, unless the cardiovascular or central nervous system is shown to be involved. The worker should not be discharged unless he refuses to remain under treatment until he has received the maximum benefit. The worker is an asset as long as he can produce, and he can produce as long as he is under treatment.

It is necessary that there should be a complete agreement between the employers and labor organizations upon any program set up. Leaders of both the American Federation of Labor and the Congress of Industrial Organizations have given wholehearted endorsement to the national syphilis program, but they are disinclined to recommend the active cooperation of their members when pro-

tection against discrimination is assured. If employers recognize the industrial and the community hazards of uncontrolled venereal disease, there need be no difficulty here. Every effort should be made to impress the workers with the facts about venereal disease, and the educational program should include information concerning prophylaxis.

Results of the campaign against syphilis

Prophylax. antivén., Paris, 12: 278, Nov. 1940.

The following statistics are cited to show the effect of the campaign against syphilis on stillbirths, infant mortality, and the incidence of early syphilis.

In 1913 there were 43.6 stillbirths per 1,000 births; in 1936 this had fallen to 33.2 per 1,000. There was a decrease of 28 percent in infant mortality. In 1912-13 the morbidity from primary syphilis in the Army of the Interior was 2 per 1,000 men, but during the war the number increased to 14.2 in 1916; to 19.2 in 1917, and 20.3 in 1918. In 1922, the result of efforts to combat this disease, the incidence fell to 3 per 1,000 soldiers; to 1.5 in 1936; to 1.3 in 1937.

In treatment centers established by the public health service there was a decrease of 37.5 percent in the incidence of primary and secondary syphilis during the period from 1930 to 1937.

The activities of the Committee on Conservation of Vision. E. L. Van Buren. *J. Indiana M. A.*, Indianapolis, 34: 235-237, May 1941.

Included in the program of the Committee on Conservation of Vision of the Indiana State Medical Association have been the following: (1) Prophylaxis of ophthalmia neonatorum with adequate and uniform treatment, (2) preventive discovery, and thorough treatment of syphilis.

The program began by forming local committees in county medical societies, by publishing articles in the State medical association journal, and preparing exhibits at the annual convention of the State medical association and at the State fair.

The following resolution was adopted by the house of delegates at a meeting of the Indiana State Medical Association in October 1939:

1. That the question on the birth certificate, "Were precautions taken against ophthalmia neonatorum?" be changed to read, "What preventive for ophthalmia neonatorum did you use? If none, state the reason."

2. That legislation should be enacted specifying that only a prophylactic agent approved by the Indiana State Board of Health shall be used.

3. That 1 percent silver nitrate be used in beeswax ampules as a universal prophylactic agent for ophthalmia neonatorum at this time with the reservation that this recommendation may be changed in the future.

4. That the Indiana State Board of Health shall acquaint physicians, individuals, and hospitals with this recommendation and see that it is uniformly and easily available.

5. That the Indiana State Board of Health shall carry on a campaign of urging the prompt and early reporting of ophthalmia neonatorum as the law now specifies.

6. That the Indiana State Board of Health, through the local health officers, shall ask the prompt reporting of conjunctivitis of the newborn from whatever organism, and shall have jurisdiction over these cases, in investigating and insuring adequate diagnosis and treatment until they are definitely classified as not being ophthalmia neonatorum. That investigation should be the direct responsibility of the Indiana State Board of Health and assured thereby.

7. That consultation with oculists be urged in these cases whenever such consultation is available. That provision be made for expert ophthalmologic and nursing care whenever necessary and that these services be arranged without delay and be available also for similar emergency cases occurring at a later date.

The incidence of ophthalmia neonatorum in Indiana is very high. Fifteen

percent of the children in the State blind school are blind because of this disease. Of those on the blind pension rolls in Indiana, 2½ percent are blind from ophthalmia neonatorum. Very few of the cases are reported, yet in one Indiana city with 100,000 population, hospital records show 10 such cases within the past 5 years. In order to stamp out this disease, these cases should be reported and adequate ophthalmologic and nursing care should be available.

Eight percent of those on the blind pension rolls in Indiana are blind from syphilis. The present syphilis program will do much to reduce this figure, and Indiana physicians are urged to prevent, discover, and thoroughly treat syphilis. Prenatal blood serologic tests would do much to prevent interstitial keratitis and optic atrophy.

Case control methods in dispensary gonorrhea. Rogers Deakin and Morris S. Wortman. *Am. J. Syph., Honor. & Ven. Dis., St. Louis*, 25: 265-269, May 1941.

Case control refers to all contacts with the patient designed to assist in the study, treatment, and control of gonorrhea. The authors believe that adequate case control includes at least the following three activities: (1) The establishment of a definite routine of gonorrheal therapy; (2) the keeping of complete, unbiased medical records of clinical and bacteriologic findings, so recorded as to allow accurate comparison of treatment procedures; (3) the use of case-holding services that will keep patients under medical observation until they have satisfied rigid criteria of cure.

Efficiency in case control can be achieved if qualified personnel is used and if there is coordination of clinical, bacteriologic, case-holding, and clerical services. Responsibility for directing and coordinating these various services should remain with the clinician.

Organization of this kind was established in the genito-urinary section of the Washington University Clinics on July 1, 1938. During the following 22

months, 474 unselected male patients were treated for gonorrhea. Of this group, 330 (74 percent) have remained under treatment until cured, or are still under observation. The average period of treatment and observation was 4½ months. Only 47 (10 percent) were lost. The remaining 16 percent were transferred to other treatment centers, returned with reinfections, left the city, or could not attend the clinic. Prior to July 1938, patients remaining under treatment until cured constituted less than 3 percent of the total number. Some clinics have reported a lapse-rate in treatment as high as 100 percent.

The authors discuss six case-holding technics, as follows: (1) Developing a congenial personal relationship with the patient; (2) conducting a social study; (3) collection of important data; (4) education of the patient; (5) stimulation of patient by keeping him constantly aware of the clinic's interest in his personal welfare by means of clinic interviews, home visits, letters, and telephone calls (of the 474 patients only 14, or 3 percent, did not require stimulation of one kind or another); and (6) case work. Proper use of these technics will keep the majority of patients under treatment.

Important to effective relationship with the patient is the maintenance of an understanding, uncritical, and noncoercive attitude. Assumption of authority, coercion, or application of compulsory case-holding methods will nearly always alienate the patient.

More identifying information than name and address is needed for maintaining contact with the patient. A recent survey indicated that of about 3,000 lapsed cases of gonorrhea reported to a State board of health, 57 percent could not be located. Identifying information obtained in the Washington University Clinics includes the following: (1) Patient's name and address (a trial letter is sent after his first visit to verify the address given), (2) name and address of his place of employment, (3) names and addresses of two people who will know how to reach the patient, (4) names of

relatives, (5) names of the patient's children (who may be traced through public schools), (6) name of insurance company with which the patient has insurance, (7) Social Security number.

Names, addresses, and other information concerning contacts and sources of infection are given much more freely on questionnaire than by personal interview. When the questionnaire has been answered, the way is opened to a personal interview.

Sociologic information about each patient (employment status, family and home conditions) is important to understanding the patient's problems. Probably no other factors are likely to influence the patient's attendance more than those within his social environment.

A study of environmental factors gives data which, when accumulated in considerable amount and properly classified, may aid in the prediction of the amount of personal contact required to effect complete cooperation of any particular patient.

Psychologic and personality factors also have important bearing on the success of personal relationship with the patient, and thus on his cooperation following treatment instructions. Fears, anxieties, and superstitions must be learned and dispelled. It is important to discover what he thinks and knows about gonorrhea. Care must be taken that he does not develop gonorrhea phobias. It seems that a gonorrheal infection can sometimes have a lasting traumatic effect on a patient's mental health. Some patients return to the clinic to inquire whether it will be all right for them to marry and have children. Others complain of impotence after their infection. It is necessary not only to attempt to remove the physical disease but the psychologic trauma as well if patients are to be discharged completely cured. Intensive case work is frequently necessary in such cases. Sometimes case work is needed before medicinal therapy can be considered.

Education of the patient is a great aid to case holding. The more closely the

ent's idea of cure approximates that of the urologist, the greater the likelihood that he will remain under treatment until he is cured.

For persons not experienced in case-ling the use of authority, legislation, force is most appealing, because it is easiest to understand and is considered effective. However, as Nelson has said, the genitoinfectious diseases cannot be dragged into the open so far as individual infections are concerned, because they are too easily hidden. Publicity and general application of compulsory methods drive them completely under cover. Often is it assumed that a summary order to return to treatment will have the desired effect."

The treatment of gonorrhea is complete which fails to treat the patient as a whole, and to take into consideration sociologic, psychologic, and environmental factors.

Cases of blindness in Hawaii. W. John Holmes and Grace C. Hamman. *Arch. Ophthalm.*, Chicago, 25: 643-650, Apr. 1941.

The number of blind persons in Hawaii at present is estimated to be 400. In this report, the authors summarize data from the case records of 379 of the 400. Of these, 340 were examined by ophthalmologists. The remaining 39 were persons known to be blind who had been repeatedly examined by medical social workers trained for ophthalmologic work, but who refused to return for a check-up by an oculist. The group of persons known to be blind constituted less than 1 percent of the total population of Hawaii. It included representatives of all principal races and racial mixtures found in the territory.

It was impossible to determine the exact etiologic factor in each case of blindness. Several patients with sunken deformed bulbs or with empty sockets were seen years after a condition primarily responsible for their blindness had abated. Inquiries by medical social workers elicited the exciting cause in several of these cases, but

sometimes the diagnosis was a matter of conjecture, arrived at by piecing together fragments of inaccurate statements given by the patient, his relatives, or his friends.

Syphilis caused 12.36 percent of the cases of blindness in this group—more than any other infectious disease. This figure corresponds roughly to the findings in other studies. Cowan and Sinclair reported that of 6,000 applicants for pensions for the blind in Pennsylvania, 9.4 percent had syphilis (*J. A. M. A.*, 107: 757, Sept. 5, 1936).

Gonorrheal ophthalmia accounted for 2.34 percent of the blindness in this group. This figure is extremely low and compares favorably with the much higher incidence of blindness from this cause in other localities. It is possible that many of the persons reported as congenitally blind really had had gonorrheal ophthalmia at birth. The National Society for the Prevention of Blindness has reported a yearly constant for the past 8 years of 7 percent for blindness caused by ophthalmia neonatorum among new students seeking admission to schools for the blind in the United States and Canada (*Sight-Saving Rev.*, 9: 126, June 1939).

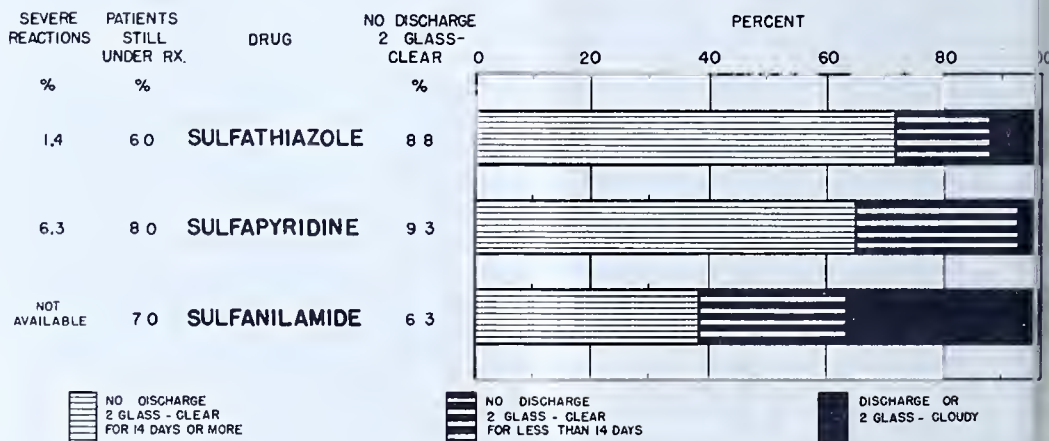
Diseases of the cornea were the most frequently diagnosed ocular derangements which resulted in blindness. Syphilis, leprosy, and trachoma, all diseases with a predilection for involvement of corneal tissue, were responsible for the high incidence of cases in this category.

Invasion of the optic nerves and visual pathways which resulted in atrophy of the papillae occurred in 13.43 percent of the cases in this group. Under this heading were grouped all cases of atrophy of the optic nerve, irrespective of cause.

The authors submit this study with the hope that it will stimulate further medical research on the causes of diseases resulting in blindness and that it will stress the importance of thorough examinations and carefully prepared case reports.

RAPID APPRAISAL OF SULFONAMIDE DRUGS IN THE TREATMENT OF GONORRHEA IN THE MALE MONTHLY REPORT

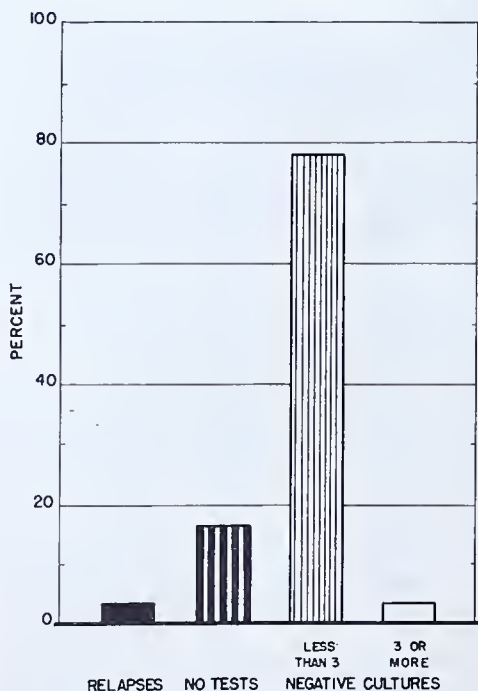
DISAPPEARANCE OF SYMPTOMS BY END OF FOURTH WEEK OF OBSERVATION



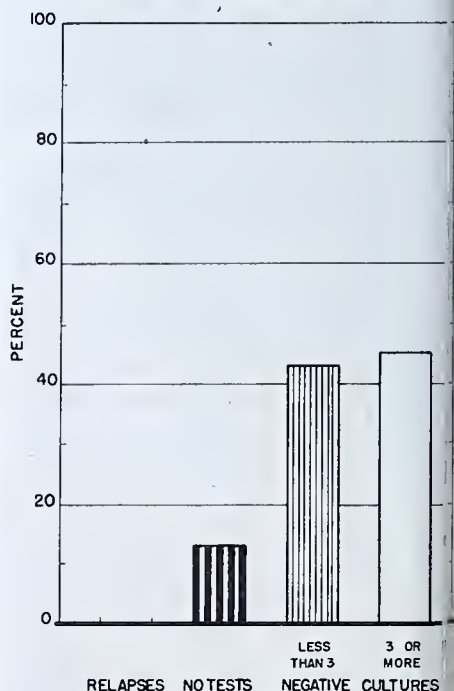
SULFATHIAZOLE

LABORATORY FOLLOW-UP IN INDICATED PERIODS ON PATIENTS SHOWING NO DISCHARGE AND CLEAR 2 GLASS TEST FOR 14 DAYS

STATUS AFTER TWO WEEKS' FOLLOW-UP



STATUS AFTER THREE WEEKS' FOLLOW-UP



NEW DRUGS

RAPID APPRAISAL REPORTS ARE PUBLISHED EACH MONTH ONLY FOR DRUGS IN GENERAL USE. RESULTS WITH NEW DRUGS INTRODUCED FOR CLINICAL EXPERIMENTATION ARE COMMUNICATED DIRECTLY TO THE RESEARCH CLINICS AND TO THE PHARMACEUTICAL LABORATORY MANUFACTURING THE DRUG. THIS INFORMATION IS AVAILABLE TO OTHERS UPON REQUEST.

The Technic of Induced Malaria as Used in The South Carolina State Hospital

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THIS PAPER was prepared in response to numerous requests for information concerning the procedure followed at the Williams Malaria Research Laboratory where malaria infection is employed in the treatment of neurosyphilis. This information has been gathered from our experience in the use of malarial therapy over a 10-year period.

METHODS OF TRANSFERRING THE INFECTION

There are two primary methods of transferring the infection from one patient to another. The one widely used because of its simplicity is the transfusion of blood from a malarious donor to the recipient. The second, and more natural way, is through the bite of infected mosquitoes. This method requires the setting up of an insectary to breed the mosquitoes, or an arrangement for obtaining the insects from some established insectary. Adult female mosquitoes are permitted to feed on a malarious patient whose blood gametocytes have been demonstrated. After the feeding the mosquitoes must be cared for under carefully controlled conditions for from 10 to 30 days while the extrinsic cycle of development of the plasmodium occurs, the completion of which is proved by the presence of sporozoites in salivary glands dissected from some of the mosquitoes. The mosquitoes are now able to transmit the infection by biting.

From the National Institute of Health, Malaria Investigations, Williams Malaria Research Laboratory, located at the South Carolina State Hospital, Columbia, S. C. The authors express their appreciation to the staff of the South Carolina State Hospital for their cooperation in the malaria work.

¹Deceased April 30, 1941.

Several mosquitoes are allowed to bite the patient, the infection developing from 10 to 20 days thereafter, depending on the species of malaria. *Plasmodium falciparum* (estivo-autumnal malaria) has the shortest incubation period and *P. malariae* (quartan) the longest.

Infected mosquitoes can be shipped successfully by placing them in a wire cage wrapped in moist cloths and enclosed in a cardboard mailing tube.

There is another method which shows promise and avoids shipping mosquitoes. In this method the infected salivary glands of the mosquito are removed under aseptic conditions and put into sterile sodium citrate. This suspended sporozoite material can then be iced, shipped, and inoculated in the identical manner in which blood is used (Mayne, 1933). The sporozoites thus prepared have been shown to remain infective for at least 26 days (Mayne, 1935).

An advantage of this method is that infective material can be transferred over long distances, as has been demonstrated by the successful transfer of such materials from this station to the Horton Mental Hospital in England, and the reverse, with "takes" after a 9-day period en route. Another advantage is that the dosage of sporozoites can be determined more accurately than can be done in the employment of living mosquitoes. At present this method of inoculation is too expensive to be universally employed. However, it adds another source of available infective material for *P. vivax* or *P. falciparum*. This method is not practical with quartan malaria as both the extrinsic and intrinsic incubation periods are too long, and the mosquito infection rate is too low.

SELECTION OF TYPES OF MALARIA

The selection of the species of malaria parasite in institutional therapy is often fortuitous, depending upon the type available at a particular moment. However, in a large institution where the number of patients makes it possible to maintain several species of parasites at one time, the type of malaria can usually be selected judiciously according to the needs of the recipient. All three species of malaria parasites indigenous to this country have been successfully used for malarial therapy.

Plasmodium falciparum (subtertian, estivo-autumnal, malignant tertian malaria) is the most difficult to control and has not found wide use as a therapeutic agent.

Plasmodium vivax (tertian malaria, benign tertian) is widely used, especially in white patients. The advantage of this species is that it runs a relatively rapid course with paroxysms every other day (tertian), frequently every day (quotidian), thus lessening hospital expenses. Unfortunately it also has several disadvantages. In the malarious part of the country many patients will exhibit an immunity to *P. vivax*, having been infected with it previously. In Negroes tertian malaria does not develop with any degree of success. Tertian malaria also has a tendency toward self-termination before the desired number of paroxysms has been experienced, and often, because of the frequency of the paroxysms, rapid debilitation of the patient occurs and the infection must be aborted (see addendum).

The third species, *Plasmodium malariae* (quartan malaria) is preferred for therapy by many clinicians. This type has several advantages:

1. Few white patients show an acquired immunity and Negroes are usually susceptible.

2. The paroxysms occur every third day, allowing the patient the most time between paroxysms. Consequently debilitation does not occur as rapidly as with the other types.

3. The natural course of the infection is sufficiently long to give a large number of paroxysms. The sole disadvantage is the length of time required.

Quartan malaria apparently is the malaria of choice when time is not a deciding factor.

SELECTION OF DONORS

When several donors are available, that one ordinarily is selected whose attacks have been most regular, who has a single-brood infection, and who has the same type of blood as the recipient. Blood typing is not generally advocated.

DRAWING AND PRESERVING THE BLOOD

Malarial blood to be kept before use must be treated to prevent clotting. It may be drawn by any of the commonly used methods. At this laboratory a large syringe with a by-pass valve between the syringe and the needle is used. The syringe is filled with blood, the valve is turned and the drawn blood forced through a tube connected with the by-pass valve into a receiving flask.

The blood in the receiving flask may be treated in one of two ways. Either it can be defibrinated by shaking with glass beads for 10 minutes, or an anticoagulant can be used. Both methods have been employed here. We find a satisfactory anticoagulant to be 2.5 percent sodium citrate in the proportion of 7 cc. of the citrate solution to 500 cc. of blood.

Following the drawing of the blood it is immediately put up in small serum vials, usually containing 5 cc., for storage or shipping. An extra protective rubber cap is put over the ordinary cap of the serum bottle. These vials are then stored in a refrigerator at about 40° F. until needed. With this method blood will remain infective up to a maximum period of 14 days, especially if the parasites are numerous.

SHIPPING THE BLOOD

Infective blood has been shipped successfully from this station to some of the most distant points in the United States. Two methods proved satisfactory:

1. The vials of blood are packed in rubber finger cots, wrapped in gauze, and then packed securely in crushed ice in a wide mouth vacuum bottle. The bottle is then placed in a specially made shock-absorbing cardboard container. The main objection to this method has been the leakage of some of the containers despite all possible care in packing.

2. A less expensive method and one that appears to be quite satisfactory makes use of the Army Medical School water-shipping containers. These consist of an inside water-tight, metal, screw-top tube 2 inches in diameter and 8 inches long and an outside cardboard screw-top mailing tube. The vials are wrapped as above and packed tightly in crushed ice in the inside metal container. Successful shipments have been made from Columbia, South Carolina, to points as far distant as Seattle, Washington; Miami, Florida; and Bangor, Maine.

INOCULATION OF PATIENT

Various methods of injecting the blood into patients have been advocated by different workers. These include scarification, and injection by intramuscular, subcutaneous, and intravenous routes. The intravenous method is routinely practiced at this hospital. Reaction is rare and when it occurs is usually manifested by a slight elevation of temperature.

When the donor and recipient are in the same ward, fresh whole blood is used. The patients are placed side by side, a needle is inserted into a vein of the donor, 5 to 10 cc. of blood (depending upon the number of parasites present in the blood of the donor) are drawn, the needles are changed, and the blood is quickly injected into the recipient before it has time to clot. This method has been found to be very successful.

In using citrated or defibrinated blood for injection, the vial is warmed to body temperature, shaken thoroughly, the cap sterilized with iodine and alcohol, the needle plunged through the cap, the blood drawn into the syringe and injected into the vein of the patient. Usually 10 cc. of blood is used.

When a culture of sporozoites is used for this purpose, the materials are handled exactly as in the case of citrated blood, and injection is made intravenously.

PREPATENT AND INCUBATION PERIODS

The *prepatent* period is the interval between the inoculation of the patient with malaria parasites and the first appearance of the parasites in the blood stream; the *incubation* period is the period from the inoculation to the first clinical symptoms of the disease. In malaria induced by blood inoculation these are seldom identical as careful observation of the blood smears often will reveal parasites 1 to several days in advance of the symptoms. This difference in time will be greater in direct proportion to the immunity that the patient exhibits to the infection. The existence of a difference between these two periods is helpful to the physician as he is warned by the appearance of the parasites of the approaching clinical attack.

Both the prepatent and incubation periods will vary according to the number of parasites inoculated, the species of malaria, and the resistance of the patient to the disease. It is possible, however, to assign approximate values for these periods.

Assuming the presence of a moderate number of parasites in freshly drawn blood, the incubation period will normally require about 1 week in tertian malaria, usually under 1 week in estivo-autumnal, and from 10 to 30 or more days in quartan malaria. The longer the blood is stored, in the refrigerator or because of shipping, the longer will be the incubation period. It is not unusual for shipped blood to require as long as 1 month to produce symptoms; the incubation periods average 3 weeks.

Unless it is desired to introduce more than one brood of parasites into the patient, thus causing the irregular appearance of paroxysms, additional inoculations should not be made during the incubation period. However, should it be desirable to have paroxysms occurring more rapidly than would be expected

from one brood of parasites, additional inoculations may be made.

NUMBER OF PAROXYSMS

The number of paroxysms necessary for optimum results is still not a matter of unanimous opinion among clinicians. Numbers varying from 8 to 20 or more have been advocated. Many workers believe that from 15 to 20 paroxysms give the best results. At this hospital we usually allow up to 20 paroxysms if we think the patient can withstand this amount of treatment. As many as 25 or 30 paroxysms are allowed for Negroes.

Occasionally a full course of paroxysms cannot be borne by the patient at one time. In such instances the infection is temporarily aborted by one dose of 10 grains of quinine, or permanently terminated by the full quinine treatment as described in a later paragraph. The administration of 10 grains of quinine will usually result in an afebrile period of 7 to 10 days. The rest period allows time for the physical condition of the patient to improve. The patient then may be allowed to have further attacks, either by relapse in the event of temporary termination or by reinoculation if the termination was permanent. In the latter event, a different species is used.

Often the malaria infection, especially the tertian, will terminate itself before the desired number of paroxysms has been experienced. In such cases the patient can be reinoculated with a different species of parasite to complete the course. In our experience, quartan malaria is the most constant in giving a satisfactory number of paroxysms before the infection is self-terminated. In white patients, when the tertian infection terminates itself, reinoculations can be made with quartan. However, in the few cases found where the quartan will not give enough paroxysms in Negroes, estivo-autumnal must be used to finish out the series, as tertian will seldom produce a satisfactory infection in this race.

CARE OF MALARIOUS PATIENT

Once a patient has been inoculated with malaria he should receive the best attention and should be kept in a ward where nurses and doctors have special knowledge in the handling of such patients.

The patient should be exposed neither to the hot sunshine nor to sudden changes in temperature even though he has a feeling of well-being on the afebrile days. In mental hospitals where some patients aid with the work in the ward, the malarious patient should not be allowed to work on the paroxysmal days and should exert himself very little on other days. The patient under malarial therapy may remain ambulant until the fever starts but then should go to bed.

While undergoing paroxysms the patient should be treated symptomatically. During the chill extra covers should be provided. During the febrile period temperature-reducing measures, such as sponging and drinking plenty of cold water, should be employed, especially when the fever is in the region of 104-106° F.

In order to replace some of the salts which are lost during the sweating periods, it has been our practice to administer 10 grains of sodium chloride on the days on which the paroxysms are expected. Sodium chloride is also given any day when the temperature goes to 101° F. or over. Salt seems to aid definitely in resisting the debilitating effects of the attacks.²

The patient should be put on a high vitamin and high caloric diet. Flus should be given in generous amounts. Apparently the sodium chloride aids in this direction as it makes the patient thirsty and more cooperative in the taking of fluids.

During hospitalization the temperature, pulse, and respiration should be checked routinely every 4 hours and hourly during

² This procedure was suggested by Dr. Irman S. Judd of the Western State Hospital at Fort Steilacoom, Wash.

ing paroxysms. The time and duration of the chills should be noted. At regular intervals the erythrocytes, white blood cells, and malaria parasites in the blood should be counted, and urinalysis carefully performed. The spleen should be periodically examined and the weight of the patient checked from time to time. The principal indications for termination of the infection are sudden overwhelming infection with parasites, severe anemia, unremitting pyrexia, rapidly enlarged and tender spleen, extreme exhaustion, cardiac disturbances, cyanosis, edema, convulsions, renal disturbances, marked increase in blood urea, development of another infectious disease, severe jaundice, and rapid debilitation involving loss of weight.

TERMINATION OF INFECTIONS

Both atabrin and quinine have been used with success in the treatment of induced malaria. In our cases the infection is terminated routinely with quinine. The patient is given 10 grains of quinine three times a day for 4 days followed by 10 grains a day for 8 weeks. Following or during the administration of quinine, antisyphilitic medication may be instituted.

Occasionally certain of the antisyphilitic drugs such as mapharsen have been reported to be effective against therapeutic malaria, which would permit shortening the postmalarial treatment. We have found, however, that mapharsen will not eradicate the parasites of the strains of quartan or tertian malaria used here (Young and McLendon, 1939). True, the symptoms sometimes were alleviated but, in the cases observed, the parasites remained in the blood stream and the infections were transmitted by binoculation.

In case of self-termination of the infection there are indications that the infection remains latent and that unless antimalarial drugs are used, relapses may occur. Malaria has been known to remain latent for many years.

REINOCULATIONS

Sometimes it is thought desirable to reinoculate a patient because of the failure of the first infection to cause enough paroxysms. In these cases usually a different species of malaria parasite is indicated for the second inoculation as the first infection will often result in high immunity to the particular strain used.

SPECIAL MALARIA WARDS

Patients undergoing malarial therapy should be kept isolated in a malaria ward with a special nurse and attendant. Where this is not possible they should at least be kept in a screened room.

The malaria ward should be well screened with metal mosquito-netting wire having at least 16 meshes to the inch. The screens should be inspected periodically and repaired if they are not insect proof. Naturally, the doors to the wards must be protected by screens. The premises for a distance of one-half mile should be given sanitary policing to prevent the propagation of anopheline mosquitoes.

Sometimes it is said that certain strains of malaria used for therapy do not exhibit gametocytes and, therefore, cannot be transmitted by the mosquito. We have had the opportunity to examine some of the strains of malaria claimed to be free of gametocytes and found that they have not differed in the ability to produce gametocytes from any other strain and were potentially just as dangerous. It has been advocated on the theory of gametocyte-free strains that patients be allowed to return home while undergoing malarial therapy. Of course, this should not be tolerated any more than should the distribution of any other cases of infectious disease among the population. The fact cannot be stressed too much that all patients with therapeutic malaria **MUST BE KEPT IN SCREENED WARDS**. This is emphasized because of reports from Europe of outbreaks of malaria because anopheline mosquitoes easily got to

patients undergoing malarial therapy. By using reasonable care such occurrences can be prevented.

CONTRAINDICATIONS

There are certain conditions which most clinicians accept as contraindications to treatment with induced malaria. These are (a) the presence of any chronic infectious disease, (b) cardiovascular or renal disease, (c) severe emaciation, (d) "galloping paresis," (e) severe anemia, (f) liver dysfunction, (g) senility, and (h) extreme obesity.

In general it is recognized that the patient who has the best chance of realizing improvement from malarial therapy is one who is young and strong and who has early neurosyphilis. For the old, the weak, and those with long-standing neurosyphilis, malaria might be employed with the hope of doing some good, but with the knowledge that the prognosis is not favorable. Even in such cases, however, malarial therapy, especially quartan, has sometimes rehabilitated those who seemed beyond hope.

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No attempt has been made to incorporate in this paper detailed clinical and laboratory findings in the malarial therapy of neurosyphilis. The medical literature on these subjects is extensive. The abridged list of references given below will indicate some of the work on the subject of therapeutic malaria, both in the clinical and parasitologic fields. In addition to the references listed, it is suggested that the numerous reports of M. F. Boyd and his coworkers, and of W. L. Bruetsch and M. A. Bahr be consulted.

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ADDENDUM

Recently a method of converting *Plasmodium vivax* quotidian paroxysms to tertian periodicity has been employed successfully at this and other hospitals. The intramuscular injections of 0.1 or 0.2 g. of thiobismol (sodium bismuth thioglycolate) 24 hours before a paroxysm is expected usually prevents the occurrence of it and of subsequent paroxysms caused by that brood of parasites. The other brood of parasites producing paroxysms at multiples of 48 hours from the time of injection of the drug is not affected. The converting of quotidian paroxysms to tertian is of much value as in some cases the patients cannot withstand daily attacks but can tolerate paroxysms every other day.

The Indications for Therapeutic Malaria in the Various Forms of Neurosyphilis

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FOLLOWING THE introduction of inoculation malaria into the treatment of general paresis, attempts have been made to extend this method of treatment to other forms of neurosyphilis and to formulate the scope of indications for its use. On the basis of my own experience as well as numerous reports in the literature, it can be said that there is still considerable uncertainty on the subject. Not infrequently cases of various types of neurosyphilis are rather indiscriminately subjected to malarial treatment. It seems worthwhile, therefore, to discuss in some detail and in the light of the clinical experiences of the last two decades the indications for malarial treatment in the various forms of neurosyphilis.

For this purpose it seems proper to classify neurosyphilis in two main groups: (1) Interstitial or meningovascular neurosyphilis, and (2) parenchymatous, so-called para- or metaluetic, neurosyphilis. The first group, that of interstitial neurosyphilis, includes the following types: Syphilitic meningitis (with or without cerebrospinal involvement), syphilitic endarteritis, and gumma of brain and spinal cord. In these types, the pathologic process originates in the mesodermal tissue, namely the meninges and the vessel walls, while the nervous ectodermal tissue becomes involved only secondarily. This group, therefore, is also spoken of as a mesodermal neurosyphilis. The second group, that of parenchymatous neurosyphilis, includes general paresis, tabes dorsalis, and primary (genuine) optic atrophy. In the types of the latter group two pathologic processes occur which apparently are independent of each other. They are a degenerative process in the functioning nervous tissue

(ganglion cells and nerve fibers) and an infiltrative-inflammatory process in the interstitial tissue, namely, the meninges and vessel walls. Because the destructive process appears to affect the neural structures primarily, this type is also referred to as ectodermal neurosyphilis. Although this division is an artificial one and although transition forms between these two main groups no doubt occur, there are enough characteristic differences to warrant such a classification. These differences, which cannot be discussed in this limited space, involve considerations of various aspects, such as pathologic-anatomic, parasitologic, biologic, serologic, and symptomatologic findings as well as the interval between the syphilitic infection and the onset of neurosyphilis, and, last but not least, therapeutic response.

In regard to the latter, experience has shown that the manifestations of the mesodermal form of neurosyphilis are influenced favorably (depending, of course, upon the stage of the disease) by the usual antisymphilitic drugs. However, those of ectodermal neurosyphilis, especially of general paresis and of primary optic atrophy, have proved definitely resistant to specific treatment alone. For this reason investigators have been searching for other methods of treatment with which better results in parenchymatous neurosyphilis, especially in general paresis, might be attained. Thus, by means of experiments inaugurated by Wagner-

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Jauregg nearly half a century ago and continued over many years by him and his associates as well as other workers, the so-called nonspecific methods of fever and infection therapy have been devised, the most effective of which is therapeutic inoculation malaria in its present form.

Both historically and according to their comparative therapeutic value, the nonspecific methods of treatment can be classified into the following groups: (1) Nonbacterial products, such as sodium nucleinate, peptone, casein, milk, phlogetan (an albuminoid), sulfur preparations. (2) Avirulent bacterial products, such as old tuberculin, polyvalent typhoid vaccine, saprovisan (mixed saprophytes), pyrifur (B. coli derivative). (3) Induction of certain infectious diseases through inoculation with living organisms, such as malaria, relapsing fever, rat-bite fever. (4) Induction of fever without recourse to either foreign protein or infection, that is, by means of various physical procedures, such as the hot bath, the hot cabinet, diathermy, radiothermy, and the like. As I have stated in previous publications, many years' experience has shown us that the virulent infectious disease, especially benign tertian malaria, ranks first in therapeutic efficiency. The avirulent bacterial derivatives, preferably polyvalent typhoid vaccine, are second and the nonbacterial products, third. As to the efficacy of physical pyretotherapy, which has come into use in relatively recent years,² this method, in my experience, is at best apt to occupy a place between the second (e. g. typhoid vaccine injection) and the first (induction of malaria) grade of the scale. It does

not, however, attain the efficiency of therapeutic tertian malaria in regard to curative results.

From this short résumé³ it is evident that malarial therapy of neurosyphilis finds its foremost indication in cases belonging to the ectodermal group, and especially in general paresis, which is the proved most resistant to purely specific therapy and insufficiently amenable to nonspecific avirulent procedures. Hence, malarial therapy is the method of choice. It has stood the test of time and experience as a potent means of producing on the one hand clinical recovery to the best possible extent in any individual case, and, on the other hand, of effecting destruction of the spirochetes in the brain, arrest of the histopathologic process (with regression of the inflammatory changes) and return of the cerebrospinal fluid to normal. The degree of the former and its ratio to the standard of the latter are dependent on the amount of anatomic survival of the functioning brain structures⁴ following treatment, and, consequently, on the varying mental levels at which the progress of the degenerative cerebral disease is arrested. Hence, malarial therapy, in connection with follow-up specific treatment with neoarsphenamine or tryparsamide and the like, should be instituted in general paresis under given conditions as early in the disease as possible. In this regard, there is a general if not universal consensus of opinion at the present time.

In tabes dorsalis, the type of painchymatous neurosyphilis which ranks

² Some authors appear to believe that the height and duration of fever induced with therapeutic malaria cannot be as accurately controlled as the hyperpyrexia induced by use of mechanical methods. This is not in accordance with our experience. While physical pyretotherapy seems not to be entirely without danger, the modern technic of malarial therapy provides a series of precautionary measures and of important advances in the management of the induced infection which, if practiced expediently, are, in my opinion, apt to render inoculation malaria (benign tertian or quartan) a safe procedure.

³ A detailed review of the history of fever and infection therapy can be found in the first chapter of my book "Die Malariaabehandlung der progressiven Paralyse." Second Edition. J. Springer, Vienna, 1928.

⁴ If within the central nervous system the functioning neural structures are affected to the point of actual degeneration of their elements, regeneration does not occur. But nerve cells which are only in a toxic or even edematous condition, may possibly recuperate. Therefore, the cases of general paresis in which complete recovery can be achieved are those which are subjected to malarial therapy before irreparable damage has been done to the brain.

closest to general paresis, the situation is decidedly different in regard to the indication of malarial therapy. In this condition malaria can by no means be called the method of choice. With the usual specific treatment employed either alone and by any route, or in combination with the milder nonspecific methods like old tuberculin, polyvalent typhoid vaccine, or other pyretogenic substances, the progress of tabes, especially if it is in an early stage, can frequently be arrested and negative findings in blood and cerebrospinal fluid can be obtained. Such an arrest of the process is, practically speaking, the only obtainable aim of therapy in any case of tabes and occasionally may occur spontaneously. Tabes does not generally show the same resistance to specific methods alone as does general paresis. Furthermore, tabes as a disease process does not as a rule show the same kind of progression as is common for general paresis. Since the course of tabes is usually more or less protracted, the milder and by no means ineffective measures can be tried first. Only if the therapeutic result is unsatisfactory in that the clinical manifestations progress in spite of treatment or that the fluid findings show no tendency to reverse, is there a definite indication for malarial therapy in tabes. Therapeutic malaria can be expected to produce the result which has not been obtained with less drastic methods. Of course, there are some cases of rapidly progressive tabes with marked cerebrospinal fluid changes in which malarial therapy should be given at once.

The indications in the treatment of primary (genuine) optic atrophy are still different. In this condition, as in tabes, the only attainable aim of treatment is the arrest of the pathologic process. Naturally, treatment must be instituted at an early phase of the disease, benefit is to accrue. Primary optic atrophy, however, is particularly refractory to specific methods of treatment in any amount and for any length of time, even if they are combined with nonspecific fever-producing agents, such as avirulent bacterial, nonbacterial, or physical

pyretotherapy. Malarial treatment does succeed in arresting the pathologic process and in saving useful vision in a significant percentage of cases unless the optic nerve degeneration is too far advanced. It should be borne in mind, however, that the treatment has to be carried through in modified form⁵ in order to prevent a too violent focal reaction. All too frequently in primary optic atrophy even malarial therapy fails to be effective. Nevertheless, it has been our experience that of all methods available (including subdural injections of arsphenaminized serum, mercurialized serum, and the like) the best results are to be obtained with inoculation malaria. This method, therefore, should take first place in therapeutic considerations of this disease.

In interstitial or meningovascular neurosyphilis in contrast to parenchymatous neurosyphilis, malarial therapy is not the method of choice but should be used only if other methods fail. In the vast majority of manifestations of meningovascular neurosyphilis the usual specific methods of treatment are sufficient. This is true whether the older technics are employed or whether more modern procedures are resorted to. In any case, the success will, to a large extent, be dependent upon the stage of the disease and upon the length of time that has elapsed since the primary infection. In dealing with late cases of interstitial neurosyphilis, especially those with positive serologic reactions in blood and spinal fluid, it is advisable to combine specific treatment with nonspecific methods either of the nonbacterial or the avirulent bacterial type, for example, polyvalent typhoid vaccine. If the procedure is adequate, good results can be expected in the majority of cases.

⁵ This is achieved by administration of an empirically established small dose of quinine (not more than 0.05 gm. per day) started the latter part of the incubation of induced malaria and continued during the intervals between the attacks of fever, the drug being given just before the temperature in a febrile bout is approaching normal. The aim is to prevent fever in a paroxysm from exceeding 104° to 105° F.

If, however, as happens not infrequently with late forms, certain cases of mesodermal neurosyphilis prove refractory to this scheme of treatment, therapeutic malaria is indicated, if the condition of the patient permits its use.

There is one exception to this rule. In the vascular form of neurosyphilis, especially in syphilitic endarteritis of the brain, malarial therapy as a rule should not be employed. It has been demonstrated that there is a difference between the effect of inoculation malaria on syphilitic localizations in the meninges and nervous structures and its effect on vascular localizations. In contrast to the definitely favorable influence of malaria on parenchymatous and meningeal neurosyphilis, the effect of malaria on vascular syphilis in general and on vascular syphilis of the nervous system in particular is less pronounced.

Finally, the treatment of so-called asymptomatic neurosyphilis, in other words, late latent syphilis with positive cerebrospinal fluid and negative clinical findings, will be discussed. Patients of this type, who are free from subjective and objective manifestations of nervous system syphilis, are of special interest because their abnormal spinal fluid is frequently extremely resistant to specific methods of treatment alone. This form ranks somewhat differently among the various types of neurosyphilis, in so far as it cannot be decided whether the abnormal findings in the spinal fluid indicate a primary affection of the meninges or a pathologic process latently present in the central nervous system itself. There are theoretical as well as practical justifications for regarding such patients with late latent, obstinately spinal fluid-positive syphilis as candidates for subsequent parenchymatous syphilis of the central nervous system, especially general paresis. The majority of syphilologists in whose domain, strictly speaking, this form belongs, have agreed that malarial therapy is the method of choice, since the pathologic spinal fluid in cases of this group is often very refractory to the most energetic specific treatment but responds

well to a combination of inoculation malaria and follow-up neoarsphenamine or tryparsamide as well as heavy metal administration. This view is shared by the neuropsychiatrists. There is also ample evidence to show that in this form of late latent syphilis the use of malarial therapy (with supplementary chemotherapy) is apt to prevent the development of manifest neurosyphilis, especially parenchymatous neurosyphilis.

In summarizing, it can be said that the more recent the primary syphilitic infection is and the less the nervous tissue itself has been involved, the more effectively purely specific methods will be, and the more will it be possible to bring about the desired result with such methods alone. On the other hand, the older the syphilitic infection and the more extensively the nervous tissue itself is affected, the more will it be necessary to combine nonspecific methods with specific treatment. These nonspecific methods range from simple fever-producing agents up to artificially produced infectious disease, namely benign tertian inoculation malaria.

DIAGNOSIS

Three cases of acute syphilitic nephrosis in adults. E. White Patton and Marvin B. Corlette. *Ann. Int. Med.* Lancaster, 14: 1975-1980, May 1941.

Three patients with acute syphilis have been seen at the Vanderbilt University Hospital during the past 2 years whose course justified a diagnosis of acute syphilitic nephrosis, according to the criteria of Hermann and Marr (1935).

CASE 1 was that of a 57-year-old white man who exhibited a purulent urethral discharge and generalized macular rash involving the palms and the soles. The blood Wassermann and Kahn tests were positive. He was given two injections of neoarsphenamine of 0.6 gm. with a 3-day interval between. After the second injection he noted oliguria and edema of the ankles. Albumin was present in the

urine. Under a high protein, salt-poor diet, restriction of fluids, and injections of neoarsphenamine the albuminuria rapidly disappeared. The blood tests have become negative in the following 2 years of antisyphilitic treatment.

CASE 2 was that of a Negro woman aged 22 who was admitted to the hospital complaining of backache and edema about the eyes. She denied any manifestations of early syphilis, and her blood tests had been negative 4 months previously. They were positive, however, on admission. Dark-field examination of fluid from an inguinal lymph node and from the healed scar were positive. During hospitalization antisyphilitic treatment was instituted; 20 months after its institution, the urine contained no albumin and the blood tests had become negative.

CASE 3 was that of a Negro woman, aged 19, who had discomfort on urination at the site of a nontender swelling of the left labium majorum. No history of a primary syphilitic lesion could be obtained. There was slight edema of the lower extremities, and the urine contained albumin. Blood tests were strongly positive for syphilis. Marked albuminuria persisted and she was given 2 transfusions, followed by an uninterrupted fever treatment with a rectal temperature at 41.5° C. for 15 hours. Five days after this treatment *Treponemata pallida* were found on the dark-field examination of serum from the vulval lesion. During the 4 weeks after the hyperpyrexia therapy and before arsenical therapy was begun the albuminuria entirely disappeared.

The authors feel that it was extremely unlikely that the arsenic caused the nephropathy in case 1 since the latter disappeared while the patient was receiving additional treatment with neoarsphenamine. The rapidity with which the nephropathy disappeared following the institution of antisyphilitic treatment was impressive. However, in cases 2 and 3, there was no treatment factor since the development of the nephropathy antedated the institution of specific therapy. Moreover, spontaneous remission of symptoms and signs without benefit of anti-

syphilitic treatment occurred in these cases.

The quantitative serologic test for syphilis: Its variability, usefulness in routine diagnosis, and possible significance; a study of 1,665 cases. Joseph Earle Moore and Harry Eagle. *Ann. Int. Med.*, Lancaster, 14: 1802-1814, Apr. 1941.

Quantitative serologic testing by the Eagle complement fixation technic has been under investigation in the syphilis division of the Johns Hopkins Hospital since 1928. The quantitative test has been used both in diagnosis and treatment. Two laboratories, each using the same technic and each under the joint supervision of the authors, were utilized. All new patients admitted to the clinic or seen in private practice have been routinely tested with the quantitative complement fixation procedure.

The authors summarize their findings as follows: The serum of syphilitic patients contains varying quantities of reagin. Quantitative serologic tests to determine this reagin "titer" are comparable only when carried out in the same laboratory by the same technic; and even then, the results may be modified by day-to-day variations in the sensitivity of the test.

The quantitative reagin titer of the blood in 508 patients with early syphilis, determined by a complement fixation technic, varied from 0 to 1,600 units of reagin. In primary syphilis, the mean titer was 104.3 ± 13.74 units, the median 43.2 ± 17.22 units; in secondary syphilis the mean was 179.6 ± 7.54 and the median $142.3 \pm (9.45)$ units.

In 445 patients with various forms of untreated late syphilis, the quantitative titer ranged from 0 to 1,600 units. These patients were separated into 5 groups: (a) Latent syphilis, (b) various forms of late syphilis (excluding neurosyphilis), (c) diffuse meningovascular neurosyphilis, (d) general paresis, (e) tabes dorsalis. In these groups, the mean titers ranged from 21.5 to 44.1 units, the medians from 10.7 to 25 units, i. e., sig-

nificantly lower than in early syphilis. It is suggested by these data, though not definitely proved, that patients with late latent syphilis and tabes dorsalis may have significantly lower serologic titers than patients with other types of late syphilis.

In late syphilis, previous treatment in any amount and at any time before quantitative testing significantly reduced the mean and median titers in the 712 such patients tested. This reduction was not necessarily associated with clinical improvement.

Quantitative serologic testing is of little value as a routine diagnostic procedure.

The reagin titer of the blood is not an expression of the severity or gravity of syphilitic infection in the individual patient. Enormous variations in titer are observed in all types of clinical involvement (0-1600), including both early and latent syphilis; and the reduction in titer effected by treatment is not necessarily associated with clinical improvement.

The reagin titer appears definitely to be related to the numbers of organisms present in the tissues of the host, since titers were higher in early than in late syphilis. As between various types of late syphilis, however, no such conclusion is permissible. There is no evidence available as to the possible relationship of reagin titer to the improvement of particular body tissues.

The effect of prolonged treatment on the rate of fall of reagin titer may conceivably be an expression of the immunity or resistance of the host; but even if this were true, a single quantitative test before treatment would be of no diagnostic or prognostic importance. Further studies of the behavior of reagin titer under prolonged treatment are essential to settle the possible prognostic value of such serial quantitative tests.

The authors will publish subsequent papers which will consider (a) certain extraneous factors which may influence reagin titer, (b) the circumstances in which quantitative serologic testing is known to be useful in diagnosis and treatment.

Progressive muscular atrophy and syphilis. Report of a case with interesting cerebrospinal fluid findings. Hervey Cleckley and L. E. Geeslin. *J. Nerv. & Ment. Dis.*, Richmond, 93: 460-472, Apr. 1941.

The case is reported of a 57-year-old white man with progressive muscular atrophy who was hospitalized for gastric ulcer in February 1939. The patient had had gonorrhea in 1905, and at the same time he had had a sore on his penis for which he received no antisyphilitic treatment. Several subsequent blood Wassermann tests had been negative. In 1935 and in 1936 the patient was hospitalized, and each time his case was diagnosed as progressive muscular atrophy. In 1935 examination of the spinal fluid showed marked lymphocytosis, the blood Kahn and Wassermann tests were negative, and the spinal fluid Wassermann test was negative.

In 1939 the small muscles of both hands were wasted. The bones stood out distinctly. The muscles of the forearm were generally atrophic, the extensors being more severely affected than the flexors. The shoulder girdle muscles were atrophied and wing scapulae were marked, especially on the left. Muscular weakness was proportionate to the atrophy.

His blood Wassermann test was again negative in February 1939. The spinal fluid Wassermann was 3 plus; the colloidal gold curve was 0000000000; the mastix test, 111000; the total protein, 50 mg.; and there were 180 cells in the spinal fluid. Because of the suggestively positive spinal fluid Wassermann test, the repeated finding of an increased number of cells in the cerebrospinal fluid, and the slightly atypical distribution of the atrophy (extensors of the forearms were more affected than the flexors, and muscles of the upper arm were relatively spared), diagnosis of syphilitic spinal muscular atrophy was made. The biceps and triceps reflexes and the knee and ankle jerks were increased. Because of this fact, it was thought that the pyramidal tracts were involved as well as the anterior horn cells.

In April 1939, the patient's cerebrospinal fluid Wassermann test was negative at one laboratory and 3 plus at another. The cell count of the spinal fluid was 149 (95 percent lymphocytes). Treatment with sodium iodide intravenously and bismuth intramuscularly was begun. In July 1939, the patient was much improved, stating that he had better use of his hands and arms than he had had for many years. Objectively, the patient had a slight but perceptible increase in strength of the muscles of the forearms, upper arms, and shoulders, although he still could not entirely close his hands.

The authors reviewed the literature on progressive spinal muscular atrophy and found strongly contrasting opinions concerning the frequency of syphilis as a causative factor. They state that it is not unlikely that patients thought to have primary progressive muscular atrophy after complete study may actually have syphilis and be in need of specific treatment. They believe that every patient with progressive muscular atrophy should have thorough and repeated cerebrospinal fluid examinations. They suggest that a patient who has this condition plus pleocytosis of the cerebrospinal fluid should be given treatment for syphilis.

The writers believe that careful clinical reports should be made of all cases of progressive muscular atrophy in which syphilis is suggested, and that continued neuroathologic study should be made whenever possible.

Studies of the transmissibility of syphilis. The infectiousness of the vaginal secretions and menstrual blood of syphilitic women. Harry Pariser. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 339-374, May 1941.

The author injected the vaginal secretions of 30 untreated syphilitic women into rabbits. The vaginal secretions of 7 produced syphilis in the rabbits. Five of these seven women had local cervical lesions. The duration of the clinical manifestations of disease in these women varied from about 1 week to 6½ years. The sixth "positive" result was obtained from

the menstrual blood of a secondary syphilitic woman who had no local cervicovaginal lesions. The seventh "positive" result was obtained from an early secondary syphilitic pregnant woman whose cervix was edematous, bluish, and boggy, but who presented no visible open lesions.

Initial dark-field examination in these seven cases revealed organisms in small numbers closely conforming to the universally accepted morphology of *Spirochaeta pallida* in four cases. In two cases the organisms were slightly thicker than average, but they were proved by the subsequent animal inoculation to be *Spirochaeta pallida*. In the seventh case the dark-field examination was negative. In 50 percent of the women who did not have lesions, the dark-field examination revealed spirochetes easily distinguished from *Spirochaeta pallida* unless wide latitude is permitted in the interpretation of the spirochetal form of the organism of syphilis. Of the 30 women, 76 percent had early syphilis and 24 percent had late syphilis.

The author reviews in detail the literature on (1) early syphilis of the vagina and urethra, (2) early syphilis of the cervix, (3) infectiousness of the latent syphilitic, (4) the problem of infectious relapse, (5) possible sources of misinterpretation of clinical and morphologic findings, and (6) variability of the biologic method used.

His conclusions are as follows:

1. Virulent *Spirochaetae pallidae* are discharged by the syphilitic woman into the vagina in the presence of local lesions early or chronologically "late" (more than 4 years' duration) in the course of the disease as a relapsing phenomenon.

2. In the absence of such lesions, they are discharged only through the menstrual blood of the early syphilitic or from an abnormal appearing cervix, in which cases it is probable that the lesions are present within the cervical os or uterus.

3. Infectiousness through the vagina is periodically recurrent rather than continuously present in the syphilitic woman, and it depends upon the presence

or absence of local lesions. The physiologic secretions are not infectious.

4. No data can be given as to the absolute end-point of cervical relapse, and no estimate of the frequency of this relapse is available. In this series of 30 cases, infectious cervical relapse was found to have occurred at least 6½ years after definite onset of the disease.

TREATMENT

Storage of mapharsen. Form letter.

War Med., Chicago, 1: 429, May 1941.

This form letter is issued by the Chief of the Bureau of Medicine and Surgery of the United States Navy:

(1) It has been called to the attention of the Bureau that large lots of mapharsen have deteriorated, as evidenced by a change in color. This has been particularly noticeable in tropical climates. (2) It is believed that this deterioration will be retarded by proper storage in a cool place protected from light. (3) In the future, it is suggested that mapharsen be stored in a refrigerator at a temperature of 10° C. or lower and kept in this storage until ready for use.

The trivalent arsenicals in syphilis.

Some recent advances, comparisons and evaluations. John H. Stokes and Herman Beerman. *Am. J. M. Sc.*, Philadelphia, 201: 611-625, Apr. 1941.

The authors review the literature on this subject, listing 115 references. They discuss (a) process of evaluation of arsenicals, (b) laboratory testing of the arsenicals, (c) new (and old) drugs, (d) new technics in the use of the arsenicals, (e) nonspecific uses of the arsenicals and combinations of their use with nonspecific measures.

In a previous article (*Arch. Dermat. & Syph.*, 35:78, 1937) these authors summarized the points on which the clinical tester of drugs and the practicing physician tend to query the introducers of

new arsenicals in the treatment of syphilis.

They state that in the clinical testing the following points are considered: (1) Rapidity of surface spirillicidal action and healing power; (2) evidence of standard or reasonably rapid reversal of serologic tests in early syphilis; (3) a low incidence of relapse, infectious or otherwise; (4) a low incidence of involvement of the nervous system in early syphilis; (5) good effect on resistant syphilitic manifestations and on late syphilis of the important systems; (6) ultimate curative action in man; (7) a low incidence of action.

The practitioner wants to know (a) whether the drug will injure or alienate his patient by either minor or serious action; (b) whether its administration is so complicated that it constitutes an office inconvenience; (c) whether it will cause rapid healing; (d) whether it will quickly relieve symptoms, especially pain; (e) what it will do for patients with a persistently positive serologic test in syphilis.

The experts' and public-health officers' first demand is increased "punch," whether expressed in greater efficacy from smaller doses, fewer injections for a given effect, shortened time for individual or total treatment, or greater intensity made possible by lessened toxicity. Other criteria listed in order of importance are (1) lasting or staying power, (2) stability and cheapness, (3) simplification of the route of administration, (4) precise and unvarying chemical constitution, (5) further reduction of unfavorable reaction-producing effect on the human subject.

The authors discuss the use of mapharsen, solusalyarsan, thioarsene, trisodarsen, bismarsen, sulfarsphenamine, silver arsphenamine, neoarsphenamine, and arsphenamine. They review the literature on the 5-day treatment for syphilis. They discuss the use of arsenicals in infections other than syphilis and in conjunction with fever therapy in cases of syphilis.

According to the authors, mapharsen is very effective drug, and the incidence of reactions resulting from its use is comparatively low. There has not been sufficient study of infectious relapse following its use. They do not recommend the use of solusalvarsan or thioarsene. Liver arsphenamine may cause argyria, and its use is discouraged. The weight of medical opinion is against the use of solusarsphenamine because of its serious reactions. Bismarsen is particularly useful in the treatment of children and in cardiovascular syphilis. Trisodarsen is very effective clinically, but there is a tendency for the drug to produce hemorrhagic reactions and dermatitis. Arsphenamine is considered the most effective arsenical in all manifestations of syphilis except paresis. Neoarsphenamine plus bismuth is as effective as arsphenamine.

Treatment of dementia paralytica. A five year comparative study of artificial fever therapy and therapeutic malaria in two hundred thirty two cases. Jack R. Ewalt and Franklin G. Ebaugh. J. A. M. A., Chicago, 116: 2474-2477, May 31, 1941.

The authors report a 5-year study of 12 patients with dementia paralytica who have been treated with either therapeutic malaria or artificial fever therapy at the Colorado Psychopathic Hospital and Clinic. The patients for each treatment were chosen alternately from admissions, and the postfever care was according to the same plan in all cases from both series and consisted of tryparsamide, neoarsphenamine, and bismuth compounds. The patients in the malaria series in most instances received 50 hours of fever at 104° F. or more. In the first years of the study, patients in the artificial-fever series received 50 hours of fever at rectal temperatures of 105° to 106° F., given as 10 treatments of 5 hours each; during the last 2 years they received only 36 hours of fever but at a rectal temperature of 105.8° F., given as 12 treatments of 3 hours each. No differences were found in the results from the

shorter, more frequent treatments. After the fever therapy and a complete laboratory and clinical study, the patient was referred to the out-patient department for weekly follow-up treatment. A thorough follow-up system was carried out, all of the malaria-treated patients and 66 percent of the artificial fever patients being followed for 5 years or until death.

Evaluation of results is difficult in any study. The series were fairly comparable as to classification of patients. Remission or improvement was noted in 69 percent of the artificial-fever group as compared with 58 percent in the therapeutic-malaria group. The rate of improvement during the follow-up care and the rate of relapse were approximately the same. The difference was in immediate improvement. This may be due to the two factors that patients may be safely treated at higher levels with artificial fever than with malaria, and that patients are usually in better physical condition at the conclusion of the febrile period under the former therapy. While the serologic response appeared to show a greater modification in the group treated with artificial fever, the difference in results was not great and roughly paralleled the difference in the rate of clinical remission. Careful, periodic, clinical re-examination offers the best guide for therapy and gives the most reliable data for evaluation of results.

Pregnancy and syphilis. A résumé of ten years work by the Los Angeles Maternity Service. B. J. Hanley and Lola Pedlow. West. J. Surg., Portland, 49: 247-253, Apr. 1941.

A résumé of the work done in the syphilitic dispensary of the Los Angeles Maternity Service for the years 1929-38 is presented. During the period one syphilologist has examined and supervised the treatment of these patients, and the general plan of treatment has remained the same. On Wednesday the patient receives neoarsphenamine intravenously and on Friday a heavy metal intramuscularly. One course (minimal treatment) consists of 6 injections of neoarsphenamine.

mine, totaling 2.2 gm., and 10 injections of a heavy metal, totaling 0.6 gm. There were 1,109 mothers treated during this period, and 858 live infants delivered. Of these infants, 88 were found to have congenital syphilis, 454 were normal both clinically and serologically over a period varying from 6 weeks to 6 years, and 316 could not be located for study.

When the mothers were treated during the first 5 months of pregnancy, 92 percent of the babies were normal, but only 76 percent were normal when treatment was begun after the fifth month. When the mothers received the minimal treatment (0 to 3.0 gm. neoarsphenamine) 75 percent of the babies were normal; 83 percent were normal when the mothers received 3 to 4 gm., and 94 percent when the mothers received 4 to 5 gm. A group of 38 women received heavy metal only, since they were thought to have been adequately treated before coming to the clinic or could not tolerate arsenicals; 93 percent of their infants were normal. There were 61 women who received no treatment at all; 74 percent of their babies were normal. In this group there were 54 multipara.

The five methods of examination to determine whether or not the child was infected were, chronologically: Dark-field examination of scrapings from the umbilical vein; cord Wassermann tests; gross and microscopic examination of the placenta; roentgen ray studies of the long bones; pediatric follow-up and repeated serologic tests.

This series adds further proof to the generally accepted ideas of treatment of antenatal syphilis: In order to have a normal infant of a syphilitic mother, treatment should begin in the first trimester of pregnancy and continue regularly throughout. A total of 4 to 5 gm. of neoarsphenamine, or its equivalent, should be given intravenously along with 2 to 3 gm. of a heavy metal intramuscularly. During the course of treatment, the pregnancy must not be forgotten. The patients should be observed closely for early signs of toxemia. Infants that

are normal both clinically and serologically without treatment at the age of months will remain so.

Treatment of cardiovascular syphilis

Soma Weiss. Bull. Genitoinfect. Dis. Boston, 4: 1-3, Apr. 1941.

Because the fundamental character of the lesions in cardiovascular syphilis is destructive, treatment of the specific condition is, on the whole, not satisfactory in advanced cases. In most cases slowing down the progress of the specific destructive lesions is all that can be expected. The treatment of cardiovascular syphilis cannot be rigidly schematized. In a young patient with early manifestations of aortitis but with no impairment of the myocardial reserve, antisyphilitic therapy is indicated. On the other hand, it is distinctly contraindicated for an elderly patient with an extensive aneurysm and advanced myocardial insufficiency. Between these two extremes is the group of patients for whom a combination of nonspecific and antisyphilitic treatment is usually best.

Whenever congestive failure develops in a patient with chronic syphilitic heart disease it should be treated by the customary methods before specific therapy is undertaken. Digitalis should be administered in minimal effective amount. Mercurial diuretics, especially mercuric purin, are indicated in the presence of pulmonary or peripheral congestion and edema. If only partial improvement of the congestive failure can be achieved, specific treatment with potassium iodide and mercury may be considered. Usual moderate doses of potassium iodide (0.3 to 0.6 gm. 3 times daily) are sufficient, used in conjunction with succinimide of mercury ($\frac{1}{2}$ gr. 3 times a week for 6 doses followed by $\frac{2}{3}$ gr. 3 times a week). When there is no congestive failure bismuth should be substituted for the mercury. Injection of $1\frac{1}{2}$ gr. or 3 gr. of an oil suspension of bismuth salicylate should be administered at intervals of from 3 days to a week for 2 or 3 months. The prognosis if the general condition of the patient

good, arsenicals are indicated. At first, weekly doses of 0.1 to 0.2 gm. of neosphenamine are given, gradually raising the dose to 0.3 or 0.4 gm. After 8 weekly doses, the treatment with bismuth or mercury is resumed, and such alternation may be continued for 50 to 100 weeks.

Patients with organic heart disease are susceptible to immediate toxic and, at times, fatal effects from arsphenamine. This is particularly true if there is a combination of cardiac hypertrophy, due to aortic insufficiency, and narrowing of the coronary arteries. In a few selected cases wiring of an aneurysm has benefited the patient, but this procedure should be practiced only by experts.

Antisymphilitic treatment, if administered skillfully, can not only prevent development of advanced lesions but can improve certain symptoms such as angina and may even decrease the size of the aneurysm.

Sulfonamide treatment of the gonorrheic woman in its relationship to sterility. G. Hörmann. *Deutsche med. Wchnschr.*, Leipzig, 67: 260-263, March 7, 1941.

According to the careful estimate made by Lentz in 1936, approximately half of the 1.5 million sterile marriages in Germany are a result of gonorrhea. Gottschalk estimated in 1936 that the number of births per year was decreased 35,000 to 40,000 by gonorrhea. According to the majority of authors gonorrhea is said to be the etiologic factor in 70 percent of all disease of the adnexa and in 10 percent of all gynecologic material.

The author points out that cure without sterility can be expected much more frequently with sulfonamide treatment than with local therapy alone. The important consideration with the use of sulfonamides is to start treatment sufficiently early.

The author started treating his patients with uliron in 1937 and later with albucid. At the end of 1940 an attempt was made to reexamine 80 women who had been thus treated in the period from 1937 to 1939, inclusive. Only 22 could be induced

to appear for reexamination; 4 were unable to return but sent back a questionnaire which they had been asked to fill out, and the other 54 could not be traced. The purpose of this examination was to test the patency of the tubes. Salpingography was made in 14 (in the other women this was not done for various reasons, 5 of them being pregnant, 1 having had an abortion since the gonorrheal infection, 2 had increased blood sedimentation rate). Two of the women who returned questionnaires reported that they had been pregnant since the infection. It was found that in 5 women the tubes were still patent whereas in 5 others there was partial closure of one or both tubes and in the remaining 4 both tubes were completely closed.

Further observations on gonococcal vulvovaginitis. Alfred Cohn, Arthur Steer and Eleanor L. Adler. *Am. J. Syph., Gonor. & Ven. Dis.*, St. Louis, 25: 329-338, May 1941.

A preliminary report on gonococcal vaginitis by the New York Vaginitis Research Project in cooperation with the United States Public Health Service has been published (Cohn, A.; Steer, A.; and Adler, E. L.: *Gonococcal vaginitis*, *Ven. Dis. Inform.*, 21: 208, 1940). This report described the results of the first year of study. The authors report here additional observations, bringing the follow-up period of all cases to a total of 28 weeks or longer.

A chart is presented to demonstrate the superiority of cultures over smears both for diagnosis and for determining cure of gonococcal vaginitis. As the length of observation increased and the disease progressed, or if treatment was instituted, the accuracy of diagnosis by the smear method was found to decrease considerably. The chart is based on a total of 1,070 examinations (made on 234 patients) in which smears or cultures or both were positive. Of this number, 1,058 (98.9 percent) were positive by culture, and 718 (67.1 percent) were positive by smear. There were 12 (1.1 percent) with positive smears and negative cultures, 352 (32.9

percent) with positive cultures and negative smears, and 706 (66.0 percent) with positive smears and positive cultures. Among patients treated with estrogenic substances, 53.3 percent of the positive cultures were accompanied by negative smears. Rectal cultures were far superior to smears.

More than 50 percent of the untreated patients were cured spontaneously within 13 weeks and 78.8 percent within 25 weeks. In about one-fifth of the untreated patients the carrier state developed in which occasional positive cultures occurred in the absence of clinical signs even after 28 weeks of observation. All of the patients, however, ultimately became negative.

Of the patients treated with sulfanilamide, approximately 50 percent were cured. Of these, 10 percent had recurrences during the follow-up period. Among hospitalized children treated with sulfanilamide, 68 percent were cured. When a child responded to sulfanilamide, cure occurred within 2 weeks. Prolonged or repeated treatment did not increase the number of cures. A satisfactory daily dosage of sulfanilamide was 0.12 to 0.2 gm. per kg. for 3 to 5 days, and then half of this for a total of 14 days.

Sulfapyridine was given to 43 children, and in every case the first culture taken after the onset of treatment was negative. Sinus and cultures became negative even before the discharge disappeared. In all cases, there was no discharge by the fifth day of treatment. Four children became positive again from 16 to 32 weeks after treatment. Two of these appeared to have new infections, while two seemed to have recurrences. Sulfapyridine was effective regardless of previous treatment or duration of the disease. At first large doses were used, but later the same results were obtained with a dosage of 0.066 gm. per kg. per day for 7 days. Sodium bicarbonate was given with the sulfapyridine. Only three drug reactions were noted. One child had fever; another had fever, nausea, vomiting, and headache; and the third had leukopenia.

Estrogenic substance brought about early clinical improvement, but the course

of the disease seemed to be little different from that in the untreated controls.

Rectal infections were diagnosed by the finding of positive rectal cultures in 45 percent of the patients. In none was there characteristic evidence of gonococcal proctitis clinically.

Study of the sources of infection showed that intimate contact is necessary before the infection can be transmitted. Pus containing gonococci must reach the neighborhood of the vulva to cause the disease.

Acute gonococcal salpingitis. A review of twenty-five cases. Walter M. Brunet and Joseph B. Salberg. *M. Rec. New York*, 153: 391-392, June 4, 1941

The authors review 25 cases of acute gonococcal salpingitis in which the patients were treated by the Women's Division of the Public Health Institute in Chicago during the years 1937-39. When salpingitis developed in these patients all local treatment given them for gonorrhea was discontinued. They were urged to go to bed and apply heat, preferably an electric pad. Sulfanilamide and sodium bicarbonate (40 grains each, daily) were prescribed if the patient could tolerate this dosage of the drug. The dosage of sulfanilamide was reduced if toxic reactions developed. In addition to oral medication, subcutaneous injections of foreign protein were given at 48 to 72 hour intervals, the minimum dose being 2 cc. and the maximum dose, 10 cc. If disturbing allergic reactions occurred, peptone solution was substituted. The average number of injections given this group of patients was eight, and the length of time of the treatment was 3 weeks. There was a rapid subsidence of symptoms following the use of sulfanilamide and foreign protein, and in most cases the pain was relieved in a few days.

This group of 25 patients was under treatment or observation from 9 to 36 weeks, the average being 16. Only one patient was ill enough to receive hospital care, and she recovered without surgical intervention. Six of the patients were reexamined within 12 months after being dismissed, and all were symptom-free.

in one patient there was a slight thickening of the adnexa.

The clinical symptoms of salpingitis are discussed, and the method of dissemination of the gonococcus to the pelvic structures is referred to. According to the authors, the prospects for satisfactory control of the disease and the avoidance of surgery with a sulfonamide administered orally and with foreign protein administered subcutaneously are excellent.

PATHOLOGY

Esophageal obstruction due to gummata of esophagus and diaphragm. R. H. Kampmeier and Edgar Jones. *Am. J. M. Sc., Philadelphia*, 201: 539-546. Apr. 1941.

The authors report the cases of 3 patients with gummatous lesions of the diaphragm and 1 with gumma of the esophagus. All 4 of the patients had esophageal obstruction as a result of these gummas. The authors were unable to find any record in the literature of syphilitic disease of the diaphragm producing esophageal obstruction. Gummatous lesions of the esophagus are extremely rare. The authors review the literature on the subject.

CASE 1 was that of a 48-year-old white woman who had had difficulty in swallowing for 3 months. Her husband had died of paresis 1 year before. Her Wassermann and Kahn tests were positive. Roentgenologic examination of the esophagus showed almost complete obstruction at about the midpoint of the esophagus with an irregular canalization through the area of obstruction suggesting carcinoma. Esophagoscopy revealed a constriction at about the midpoint of the esophagus. A band of scar tissue was observed in this area, below which there was a granular tumor which appeared to be carcinoma. However, biopsy revealed chronic inflammation with no evidence of neoplasm. The patient was given po-

tassium iodide and weekly injections of bismuth salicylate. After 2 weeks the swallowing had improved, and after the fourth week the patient had little trouble taking food. After seven injections of bismuth and one of neoarsphenamine; the patient was free of symptoms. Continuous antisyphilitic treatment was given until the patient had been given 66 injections of bismuth and 50 injections of neoarsphenamine. She gained 25 pounds and was greatly improved. The blood Wassermann and Kahn tests remained positive. A few months later esophagoscopy indicated an increase in the degree of constriction. The stricture was dilated 22 times. The patient eventually became entirely free of symptoms.

CASE 2 was that of a 69-year-old Negro man who had pain in the region of the kidneys, dyspnea on exertion, cough, difficulty in swallowing, and abdominal pain after meals. He had had syphilis 20 years before, and his Wassermann test was positive. Roentgenologic examination showed fibroid tuberculosis of the lungs and constriction of the terminal portion of the esophagus. The symptoms improved following deep roentgen-ray treatment. He died several months later. At autopsy it was found that the esophagus was so compressed where it passed through the diaphragm that the lumen was practically closed. This was caused by a hard tumor mass in the diaphragm which almost completely encircled the esophagus. This tumor was found to be a gumma, and it involved the medial portion of the diaphragm including the pillars and the upper medial portion of the liver. It measured 5 x 5 x 6 cm. and was nodular. A sagittal section of the mass revealed a large, irregular, orange-yellow, necrotic fibrous focus about 4 x 5 x 6 cm. in size, surrounded by a bluish-white, gristle-like capsule about 1 cm. in thickness. The entire mass seemed to be fibrous tissue with a caseous, necrotic center. The patient also had dilatation of the aortic arch.

CASE 3 was that of a Negro male, age 56. **CASE 4** was that of a Negro male,

age 24. In case 3, the patient recovered following antisyphilitic treatment and removal of the tumor mass (gumma) in the diaphragm which constricted the esophagus. In case 4, the patient recovered following a gastrotomy and antisyphilitic treatment. This patient also had a gumma in the diaphragm which constricted the esophagus.

The differentiation of gummatous lesions of the esophagus or diaphragm from obstruction due to carcinoma or cardiospasm can be made only by direct examination (esophagoscopy and biopsy), and the ultimate response to treatment. Antisyphilitic treatment for gummatous lesions producing esophageal obstruction not only may fail to relieve but actually may increase the obstruction ("therapeutic paradox"). Because of resultant fibrosis and contraction of scar tissue, esophageal dilatation will probably be necessary.

Case 2 illustrates the importance of accurate diagnosis in esophageal obstruction. The age of the patient and the results of roentgenologic examination led to the diagnosis of carcinoma and the use of palliative treatment in spite of the fact that he was known to have syphilis. Appropriate treatment at the time the patient was first seen probably would have relieved the obstruction.

It should be emphasized that esophageal obstruction in a case of chronic syphilis may be carcinomatous. Gummatous lesions of the esophagus or diaphragm are rare. In individuals with syphilis, the incidence of carcinoma of the esophagus may be greater than obstructive gummatous lesions. Accurate diagnosis and appropriate treatment are very important.

Syphilitic heart disease. Benjamin J. Clawson. *Urol. & Cutan. Rev.*, St. Louis, 45: 219-225, Apr. 1941.

During the years 1910-38 at the University of Minnesota there were 30,265

autopsies performed, and, of these, 38 (1.1 percent) were syphilitic cardiac cases. During the same period there was a total of 4,678 cardiac deaths from all causes. The incidence of cardiac syphilis (6.9 percent of the cardiac deaths) began to decrease in the 5-year period 1929-33 so that in 1934-38 there were 7.8 cases per 1,000 autopsies as compared to the average of 13.23 cases per 1,000 for the 15 years 1914-28.

Aortic insufficiency which followed the deformity of the aortic cusps or a separation of the attachments of the cusps to the aorta was the cause of death in 8 percent of the cases, narrowing of the coronary orifices in 22.6 percent, rupture of an aortic aneurysm in 20.8 percent, and gumma of the myocardium in 1.5 percent. The greatest number of deaths in both sexes occurred in the fifth decade and most of the deaths occurred in the fifth and seventh decades. None was found in the first two and the tenth decades. Syphilis of the aorta and heart was more common among the males, the ratio being 2.8 to 1. The significant differences were in the fourth, sixth, and seventh decades.

Myocardial hypertrophy was the main pathologic condition noted; it was found chiefly in the aortic insufficiency case. Little hypertrophy was noted in the hearts where death followed narrowing of the coronary orifices. This finding does not support the belief that cardiac hypertrophy may be caused by coronary insufficiency. Except in 5 cases of gumma of the myocardium little besides the cardiac hypertrophy could be found in the heart to account for the heart failure. Spirochetes were not found in any case. The narrowing of the coronary orifice was due to intimal change in the aorta. No support was found for the suggestion that syphilis is an etiologic factor in atherosclerosis. Apparently aortic insufficiency was only occasionally due to stretching of the aortic ring.

LABORATORY RESEARCH

nous injury produced by sulfanilamide and some of its derivatives in the chicken: Preliminary report. Raymond N. Beiter, A. B. Baker, J. Gordon Eaton, James M. Shaffer, Thomas M. Leery and Burton A. Orr. J. A. M. A., Chicago, 116: 2231-2236, May 17, 1941.

For this study six drugs, namely, sulfanilamide, sulfapyridine, sulfathiazole, sulfamethylthiazole, sulfanilyl dimethylthioanilamide (uliron), and sulfaphenylthiazole, were administered to young chickens with the aim of determining the extent and degree of injury, if any, produced on the brain, the spinal cord, and the peripheral nerves. For the most part the drugs were administered orally by gavage tube or in capsules, generally in doses of 0.5 or 1 gm. per kilogram of body weight once a day. Doses were continued, as a rule, for periods of 1 to 2 weeks. Despite the fact that the doses administered to the chickens were extremely high in comparison with clinical doses, the resulting levels of the drugs in the blood, with the exception of that of sulfanilamide, were not greatly out of proportion to the concentrations obtained in clinical use. The chickens were killed at the end of the period of medication and the brains, spinal cords, and sciatic nerves examined.

Sulfanilamide: The peripheral nerves of 4 out of 6 chickens showed slight injury; one spinal cord presented slight degeneration; all other elements of nervous tissue were normal. **Sulfapyridine:** The changes produced in tissue by this drug were similar to those produced by sulfanilamide. **Sulfathiazole:** Every peripheral nerve presented some injury; the spinal cords in 6 of the 11 chickens showed injuries, and the brains of 4. **Sulfamethylthiazole:** All peripheral nerves were damaged; the spinal cords of 6 and the brains

of 4 of 7 chickens showed injury. **Uliron:** The peripheral nerves showed extensive injury; in 6 of the 7 chickens, the spinal cords and the brains also showed extensive injury. **Sulfaphenylthiazole:** The most extensive injury to peripheral nerves was observed with this drug; every spinal cord and every brain showed injury. Correlation of the pathologic data with symptoms observed in chickens was difficult.

The order of the drugs studied, according to the amount of injury they produce in the nervous system of the chicken, beginning with the least injurious, is sulfanilamide, sulfapyridine, sulfathiazole, sulfamethylthiazole, uliron, and sulfaphenylthiazole.

The trend of the pathologic lesions observed in the chicken was found to have a rough parallel with the trend of clinical experience.

The concentrations of four of these drugs were determined in the various tissues. The data showed strikingly that the levels of these drugs in the organs studied show great variations from the average concentrations in the blood.

From the standpoint of the experiments on chickens and the available clinical data on peripheral neuritis, it is the belief of the authors that any one of the drugs studied may occasionally produce nervous lesions.

Two cases of peripheral neuritis possibly due to sulfathiazole are briefly described.

Urinary excretion of sulfapyridine in the rat. A relationship of the liver to urolithiasis. John V. Scudi and Harry J. Robinson. Am. J. M. Sc., Philadelphia, 201: 711-717, May 1941.

The authors report the results of studies of the urinary excretion of sulfapyridine in the rat. The rat, like man, excretes the drug in both the free and acetylated forms. They describe the procedures of their experiments in detail and review some of the literature on urinary excretion of the drug.

From the results of their experiments the authors conclude that the following steps seem to be involved in the detoxi-

cation and urinary excretion of sulfapyridine: (1) It is excreted partly unchanged; (2) part of it is rapidly acetylated in the liver and excreted as acetyl-sulfapyridine; (3) part of it is oxidized in the liver to a hydroxysulfapyridine, some of which appears in the urine; (4) part of it is conjugated with glucuronic acid in the liver after oxidation to hydroxysulfapyridine. This soluble product appears in the urine.

The dosage level was 1 gm. of sulfapyridine in aqueous suspension per kg. of body weight, daily, for 12 days. At this dosage level, it was estimated that as much as 40 percent of the free sulfapyridine may be present in the form of the highly soluble glucuronate. The glucuronic acid output was not stimulated when sulfanilamide was administered. When sulfathiazole was administered, the glucuronic acid output was intermediate between that following sulfanilamide and that following sulfapyridine.

Liver damage by phosphorus poisoning was shown to prevent the increase in glucuronic acid output following sulfapyridine administration. The incidence of uroliths was increased from 10 percent to 60 percent by phosphorus poisoning. Thus, in the rats the damaged liver was an important etiologic factor in urolithiasis.

Comparative effects of sulfonamide compounds in producing cyanosis and anemia. Arthur P. Richardson. *J. Pharmacol. & Exper. Therap.*, Baltimore, 72: 110, May 1941.

Details of methods are described by which bacterial chemotherapeutic agents may be compared for their ability to produce anemia and cyanosis in mice. On the basis of drug intake per kilo per day sulfanilamide was found to be the most injurious to blood, being 2.1 times as injurious as sulfapyridine, 4.3 times as injurious as sulfathiazole, and 10.9 times as injurious as sulfanilylguanidine. When corrections were made of differences in absorption, excretion, molecular weight, and partition between erythrocytes and plasma, the four compounds

were of approximately the same toxicity. Cyanosis, characterized by the formation of sulfhemoglobin, was observed only with higher doses of sulfanilamide and sulfapyridine.

Distribution of sulfapyridine and its sodium salt in ocular fluids and tissues after local application. S. P'an. *J. Pharmacol. & Exper. Therap.*, Baltimore, 72: May 1941 (Proc. Soc. Pharmacol. & Exper. Therap. 31).

Following a technic described elsewhere (in press) 100 mg. of finely divided sulfapyridine was applied topically to one eye of each of 8 albino rabbits. One hour after application, the concentrations of the drug in the various ocular fluids and tissues were: Conjunctiva 47.1 ± 1.2 , cornea 30.3 ± 6.0 , sclera 10.9 ± 3.6 , aqueous humour 4.7 ± 1.2 , and lens 2.4 ± 0.8 percent. The chorioretinal layers, vitreous humour, all tissues and fluids of untreated eyes, and the blood contained no sulfapyridine.

Similar determinations were made after local application of 100 mg. of sodium sulfapyridine to 8 rabbits. Concentrations of this drug 1 hour later were: Cornea 156.7 ± 22.0 , aqueous humour 88.3 ± 9.7 , conjunctiva 75.8 ± 1.1 , sclera 21.9 ± 5.7 , lens 17.7 ± 2.4 , and chorioretinal layers 11.7 ± 4.4 . No drug was found in the aqueous humour, blood, or in untreated eyes.

No tissue reactions were observed following application of sulfapyridine. In eyes to which sodium sulfapyridine was applied marked congestion and chemosis of the conjunctiva appeared almost immediately. These reactions did not subside until from 2 to 5 days after treatment.

Sulfapyridine overdosage—antidotal action of hypnotics in animals. With note on sulfathiazole. Richard K. Richards. *J. Lab. & Clin. Med.*, St. Louis, 26: 1256-1261, May 1941.

In order to secure clear-cut results with respect to toxic effects and their possible management, the authors have used their experiments in rabbits the intrav-

is injection of a 20-percent sodium sulfapyridine solution. While 500 mg. per kilogram regularly produced convulsions, 1,000 mg. per kilogram were fatal in 70 percent of the animals. A total of 1,000 mg. per kilogram always caused death from secondary depression or pulmonary edema. Higher doses, and 1,200 mg. killed the animals within a few minutes following a violent tonic or clonic convulsions. The fact that the convulsions were of the tonic type suggested that they might be combated by means of hypnotics. Urethane was used in the first experiments. The urethane was injected intravenously as a 25-percent solution mixed with 1,000 mg. per kilogram of sulfapyridine. This amount of sulfapyridine alone would kill 100 percent of the animals. The mortality was zero with the use of 5 mg. per kilogram of urethane, an amount which, by itself, has no noticeable influence on a normal rabbit. With smaller doses, the protective action against convulsions was insufficient; with larger doses, the convulsions disappeared; a general depression quickly developed which led eventually to respiratory paralysis. Attempts to antidote 1,200 mg. per kilogram of sulfapyridine with a simultaneous urethane injection were unsuccessful. The antidotal effect of sodium pentobarbital (nembutal) on sulfapyridine convulsions was studied in a similar way. In general, the effect was similar to that of urethane, but a definite antidotal action was present even against 1,200 mg. per kilogram of sulfapyridine. Death could be prevented only rarely with large doses of sodium bromide given orally. Similar experiments were carried out with dogs. It was found that 5 mg. per kilogram of nembutal added to 400 mg. per kilogram of sulfapyridine prevented convulsions but not vomiting, while 10 to 20 mg. per kilogram suppressed not only convulsions but also vomiting and other signs of subjective discomfort. Dogs in which convulsions had developed after the administration of sulfapyridine could be caused to sleep by the injection of a small amount of barbiturate. These animals recovered promptly.

It was found, therefore, that death from intravenous lethal doses of sodium sulfapyridine in rabbits and dogs occurred during or after violent tonic or clonic convulsions, and that small doses of hypnotics, such as urethane or nembutal, could inhibit the convulsions and save life. Subhypnotic doses of the urethane or nembutal were most effective, larger doses causing death by adding to the secondary depressant action of sulfapyridine. Picrotoxin can overcome the effect of this summation. Restlessness, nausea, and vomiting following large doses of sodium sulfapyridine in dogs can be completely eliminated by subhypnotic doses of nembutal.

The authors believe that the experimental results described justify the trial of sedatives in small doses in combination with sulfapyridine to alleviate irritating side effects of this drug on the central nervous system.

After this paper was completed, the authors did corresponding work with sodium sulfathiazole. They found that, principally, nembutal appears to exert the same effect in combination with sodium sulfathiazole as is reported with sodium sulfapyridine.

Studies on the role of *Spirochaeta pallida* in the Wassermann reaction. I. Complement fixation in syphilis, leprosy, and malaria with spirochetal antigens. John A. Kolmer, Clara C. Kast and Elsa R. Lynch. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 300-318, May 1941.

The authors review briefly the literature on antigens of *Spirochaeta pallida* in complement fixation tests. They report the results of their investigation of antigens from alleged cultures of *Spirochaeta pallida* (Nichols-Hough, Noguchi, Kroó, and Reiter strains), and antigens of *Spirochaeta macrodentium*, *Spirochaeta microdentium*, and *Bacillus diphtheriae* as controls in complement fixation tests. These studies were made on serums of normal persons and on serums in cases of syphilis, leprosy, and malaria.

The authors describe the strains of organisms used, the preparation of the antigens, the titration of the antigens, the tests used, and their results. The Kolmer complement fixation, the standard Kahn, and the Kline tests were employed as control tests.

As a result of these studies, the authors believe that in syphilis, leprosy, and malaria a complement-fixing antibody is to be found in the serums for antigens of alleged cultures of *Spirochaeta pallida*, but that this is a group antibody capable of fixing complement with antigens of *Spirochaeta macrodentium* and *Spirochaeta microdentium*. Normal human serums (also, to a much lesser extent, normal cerebrospinal fluids) contain this natural antibody, especially for *Spirochaeta microdentium*. This antibody is an important factor in the mechanism of complement fixation with antigens of alleged cultures of *Spirochaeta pallida*.

Because of this normal or natural group spirochetal antibody, the authors believe that antigens of alleged cultures of *Spirochaeta pallida* can yield a high percentage of nonspecific reactions in syphilis unless the amounts of antigen employed are sufficiently small to avoid them. The authors predict that the incidence of true positive complement fixation reactions with spirochetal antigens in syphilis would be far inferior to the incidence of true positive reactions observed with cholesterolized alcoholic extracts of beef heart commonly employed as antigen in the Wassermann test. They have observed no results justifying the use of spirochetal antigens in the serum diagnosis of syphilis.

The authors did not use the commercial antigen prepared of the Reiter strain of alleged *Spirochaeta pallida* known as "Palligen" and used by Erickson and Eagle. The manufacturers refuse to divulge the details of the preparation of the latter antigen, but it is apparently prepared from the same Reiter strain as that employed in this investigation. Palligen contains considerable debris which was absent in the antigens used in these studies.

A rapid slide flocculation test for syphilis. Francisco Márquez. *Am. J. Syph., Gonorr. & Ven. Dis., St. Louis* 25: 319-323, May 1941.

The author describes the technic of a slide flocculation test for syphilis which he believes has the advantage of being rapid, easy, and inexpensive. He has worked on the procedure for more than a year and has found it to be as sensitive and specific as the Kahn standard test.

Márquez compared the Kahn standard with his own test in the examination of 1,496 serums. Of 840 nonsyphilitic serums, 832 (99.1 percent) were negative and 8 (0.9 percent) were falsely doubtful with the Kahn test. With his own test, 836 (99.5 percent) were negative, and 4 (0.5 percent) were falsely doubtful. Of 656 known syphilitic serums, the Kahn test was positive in 524 (79.8 percent), doubtful in 38 (5.7 percent), and negative in 94 (14.5 percent). Márquez' test was positive in 526 (80 percent), doubtful in 40 (6 percent), and negative in 90 (13.7 percent).

The serology of syphilis and its evaluation. F. Rytz. *Minnesota Med., Minneapolis* 34: 321-326, May 1941.

The diagnostic value of the serology of syphilis has always been controversial, not because the reactions are based on unsound immunologic principles, but mainly because of intricate biologic interference with the mechanism of immunity, especially when in vitro demonstrations are attempted.

The Wassermann reaction, based on a complex immunologic factor, has become the nucleus around which other serologic methods for the detection of syphilis have developed. For the standardization of the complement fixation method, the clinical diagnosis has served as a sound basis. But it was observed that the Wassermann test failed to show positive reactions in some cases, especially in patients given antisyphilitic treatment. Sensitization efforts were attempted, with some success. Modifications of the Wassermann test have been made. The flocculation methods constitute the most reliable. The Wassermann reaction became innumerable.

ore simple and direct methods of testing, and the most sensitive of these procedures leave unrecognized but a small percentage of the syphilitic individuals tested. On the other hand, the number of false positive tests is relatively large both for the flocculation and the complement fixation method. The preparation of the antigen is of great importance.

Rytz describes a differential test and the results obtained in syphilitic rabbits and in animals showing false positive syphilis reactions. This test was privately applied to samples submitted to Rytz by the Minnesota State Serologic Evaluation Committee. There were 99 blood samples from patients with a clinical diagnosis of syphilis or from patients with positive reactions to routine pre-emptive tests for that disease, and 70 proved to have positive reactions to differential tests. That group had been treated on an average of $1\frac{1}{2}$ years. Of the remaining 29 blood samples from presumably syphilitic donors, 20 were from persons who had been treated on an average of $2\frac{1}{2}$ years and showed more or less positive routine Rytz and Kahn reactions, but the differential tests were negative. The other 9 donors had negative Rytz and Kahn reactions; the differential test, therefore, was not applied. Among 3,100 individuals presenting themselves as blood donors, 32 were found to have positive reactions to routine Rytz and Kahn tests. Of that group, 25 had positive reactions to the differential tests, and the majority gave a history of primary or secondary syphilitic lesions. The 7 cases with negative reactions to the differential tests had weakly positive reactions to routine Rytz and Kahn tests, and none had a syphilitic history.

The future serodiagnosis of syphilis will undoubtedly call for considerably more time than has been allotted for that purpose in the past. The newer form of serodiagnosis requires repeated and continuous laboratory study, depending on the clinical findings. From a serologic point of view, the first blood sample may not be found satisfactory. Neither the

result of the routine tests nor the differential reaction should be definitely interpreted on the basis of a single examination. It is in the interest of social security that syphilitic infection be arrested, but it is in the interest of social justice that as few persons as possible be subjected to a hasty and incorrect diagnosis based on misleading serologic findings. Differential and verification tests may still be in the experimental stage, but there is reason why the clinician should withhold a final diagnosis of latent syphilis in cases with negative differential tests and no other indication of the infection than a positive "routine" serologic test for syphilis.

The difference in reliability of the various routine tests for syphilis appears to be relatively slight in comparison with the general unreliability of all so-called routine tests.

The prevention of non-specific and prezone reactions in the Wassermann test with sera and spinal fluids by the addition of egg albumin to the complement. John A. Kolmer. *Am. J. Clin. Path.*, Baltimore, 11: 402-413, May 1941.

Boerner and Lukens have reported their discovery that egg albumin is highly effective in the prevention of nonspecific reactions sometimes observed in simplified and quantitative tests with normal spinal fluids (*Am. J. Clin. Path.*, 11: Tech. Suppl. pp. 71-74, March 1941). They suggested adding 0.2 cc. of a 50-percent dilution of fresh egg albumin in saline solution to each tube of the Kolmer test of spinal fluids.

Kolmer states here that he agrees with Boerner and Lukens, and he gives a simple method for employing egg albumin in solution with complement. He recommends the use of egg albumin-complement mixtures in the routine conduct of both simplified and quantitative Kolmer tests with spinal fluids. He also recommends such mixtures for Kolmer quantitative complement fixation tests employing serums, when nonspecific prezone-like reac-

tions due to complement are being observed. These mixtures are not required for Kolmer simplified tests with serums, because nonspecific reactions referable to complement do not occur in such tests.

Kolmer states that egg albumin-complement mixtures reduce the sensitivity of complement fixation reactions with both syphilitic spinal fluids and serums, but not sufficiently to reduce materially the incidence of positive reactions.

Kolmer tried complement diluted with 0.5 percent solutions of gelatin in saline solution for the prevention of nonspecific reactions with spinal fluids and serums, but the results were unsatisfactory. The more concentrated solutions varying from 1 to 10 percent could not be used because the gelatine congealed during the period of primary incubation in the refrigerator.

Observations on infectious mononucleosis. Edgar W. Warren. *Am. J. M. Sc.*, Philadelphia, 201: 483-489, Apr. 1941.

The author reports in detail the findings in 12 cases of infectious mononucleosis. He states that the whole question of antibody production in infectious mononucleosis is obscure and complex. Nonspecific bacterial agglutinins for typhoid, paratyphoid, undulant fever, and other diseases appear occasionally. Falsely positive Wassermann, Kahn, and Eagle reactions are frequent.

According to the author, two mechanisms for these findings may be postulated: (1) The antibodies may be those normally present or previously acquired in some manner; (2) the chemical and spatial structure of the antigens of the above conditions and of infectious mononucleosis may be very closely related.

With the first mechanism, a liberation of preformed antibodies could be thought to occur. In the second mechanism, either "typhoid-like" immune bodies might be produced by the antigen of infectious mononucleosis, or the heterophil antibody itself may be capable of agglutinating the bacteria.

The author states that it seems more likely that the heterophil antibodies of

infectious mononucleosis represent certain alterations in the molecular complex of the Forssman antibody. That is, the presence or development of the latter is essential for those of infectious mononucleosis.

The toxicity of bismuth salts by intravenous injection. Torald Sollmann and Joseph Seifter. *J. Pharmacol. Exper. Therap.*, Baltimore, 72: May 1941 (*Proc. Am. Soc. Pharmacol. Exper. Therap.* pp. 39-40).

Fast, slow, and repeated slow injections of water-soluble ionic bismuth compounds (sobisminol, NaBi citrate, and thiobismol) were made intravenously in rabbits and dogs in order to compare the influence of rate on toxicity, symptomatology, the sojourn of Bi in the blood and distribution of Bi in the organs.

Slow injections decreased the renal toxicity of sobisminol and NaBi citrate, that the LD₅₀ obtained for fast injection was more than doubled; but the toxicity of thiobismol appeared unaltered. Dividing the dose in equal portions and injecting slowly for 5 successive days did not further decrease toxicity in rabbits. Liability to flocculation, death decreased with slow injections, especially in dogs, except that slow injection of thiobismol appeared to be more toxic to rabbits than were the fast injections.

Deaths occurring during or shortly after injections were typical of flocculation. Animals which died later showed only the lethargy of uremia. Neither these animals nor those which were sacrificed 30 to 60 days after injection developed any of the striking features observed with administration of more freely diffusible bismuth compounds (trimethyl bismuth).

The sojourn of Bi in dogs' blood followed the characteristic rapidly descending parabolic curve of crystalloid substances, except that thiobismol when injected slowly behaved more like a colloid.

The percent of Bi in the organs paralleled the amount administered and decreased with the time elapsed after administration. Kidney and lung store Bi more rapidly than liver and spleen. The

concentrations were 15 times those obtained by intramuscular injection of similar doses of water-soluble bismuth compounds and approximately the same as with like doses of intramuscular injections of the oil suspensions.

the similarity in basic functions of various bismuth compounds used in the therapy of syphilis. N. M. Clausen, B. J. Longley and A. L. Tatum. *J. Pharmacol. & Exper. Therap.*, Baltimore, 72: May 1941 (*Proc. Am. Soc. Pharmacol. & Exper. Therap.* p. 9).

When the maximal tolerated dose (M. T. D.) determined by the intravenous route was found to be almost the same for bismuth sodium tartrate, bismuth citrate, bismuth ethyl camphorate, bismuth subnitrate, bismuth subcitrate, bismuth subborate, and thiobismol, it was decided to try to determine the minimal curative dose (M. C. D.) for each compound by the same route in rabbit syphilis. The purpose in using this route of administration is to abolish the obvious factors of absorption, thus putting the compounds on a more common basis for comparison. Using the usual method of popliteal lymph-node transfer as the criterion of cure, 4 out of 4 compounds tried were curative when fractions of the M. T. D. were given in 3 weekly intravenous administrations, each giving a M. C. D. in the neighborhood of 1 or 2 milligrams per kilogram. When the therapeutic indices are calculated from these data, each of the compounds appears to have an index between 1 and 3. Hence, methods have been presented which have better enabled comparison of the toxicity and therapeutic efficiency of various bismuth compounds on a more common basis than has been accomplished heretofore. From the data presented, further evidence has been developed to support the contention that the various bismuth compounds ultimately act in a common manner.

Damage to the optic tract produced in monkeys by tryparsamide. B. J. Longley, N. M. Clausen, F. A. Davis, M. E. Nesbit and A. L. Tatum. *J. Pharmacol. & Exper. Therap.*, Baltimore,

72: May 1941 (*Proc. Am. Soc. Pharmacol. & Exper. Therap.* pp. 27-28).

Since disturbances in vision result occasionally from the clinical use of certain arsenical drugs, it seemed highly desirable to attempt to reproduce such an action in laboratory animals. Five rhesus monkeys were treated with increasing doses of tryparsamide. Four of the 5 which received higher doses became blind. The blindness was, for all practical purposes, complete except for the light reflex, which was maintained. There was a paling of the optic nerve head and a searching nystagmus. Histologic studies are in progress. Other compounds studied include acetarsone and atoxyl. These compounds produced more muscular weakness and incoordination than did tryparsamide but, in the relatively short period of observation, have not produced blindness.

The diagnostic value of the colloidal carbon flocculation test in spinal fluid.

Paul B. Szanto, Samuel Burack and Oscar Kreisler. *J. Lab. & Clin. Med.*, St. Louis, 26: 1349-1351, May 1941.

The authors have used the colloidal carbon flocculation test for spinal fluid in cases of neurosyphilis, as modified by Schube and Harms with the exception that they found that 4 tubes gave sufficiently accurate results.

They examined 268 patients, of whom 156 had general paresis. In every non-syphilitic case the test was negative. In 141 of the 156 cases with positive spinal Wassermann reaction the test was also positive, a percentage of 90.4.

Comparison with the gold sol test showed: In 44 cases with typical first zone curve, the colloidal carbon flocculation test was always positive; in 51 cases with a middle zone curve, it was positive in 49 cases, and in 10 cases with an end zone curve, it was positive in 8 cases. In 47 treated cases with a negative Lange but positive Wassermann test, the test was positive in 36 cases. Comparison with the Takata-Ara test showed: Among 134 cases of general paresis, in 104 cases

where the Takata-Ara test was positive, the colloidal carbon flocculation test was positive in 102 cases. In 31 cases with negative Takata-Ara reaction, the test was positive in 25 cases.

From these data, the authors say that the colloidal carbon flocculation test appears to be more sensitive than the Lange and Takata-Ara tests. The test continues to be positive in treated cases of general paresis where the Ross-Jones test, cell count, and Lange test are already normal. The cases tested gave no "false-positive" results. Because of the simplicity of the test it can be used where ordinary laboratory facilities are not available.

The development of the agent of lymphogranuloma venereum in the yolk sac of the chicken embryo. Geoffrey Rake, Helen Jones and Morris F. Shaffer. (Abst. of paper given at Ann. Meet. of Am. Soc. Exper. Path., Apr. 17-19, 1941). *Am. J. Path.*, Ann Arbor, 17: 460-461, May 1941.

The agent of venereal lymphogranuloma, when introduced into the yolk sac of the developing chicken embryo, produces an infection fatal to the embryo in from 3 days to 2 weeks. Studies on the distribution of the virus by transfer to a new series of embryos by the yolk sac route show that the virus is present in large quantities in the wall of the yolk sac and in the yolk itself. The development of the agent in the wall of the yolk sac has been investigated by means of histologic sections and alcohol-fixed impression smears. The pathologic picture consists essentially of the development, within the yolk cells, of small foci of dark-staining bodies which increase rapidly in number and, concurrently, decrease somewhat in size until the cytoplasm of the distended yolk cell is filled with small particles. These bodies are apparently identical with the granulocorpuscles of Miyagawa and appear to be elementary bodies of the agent. Definite correlation has been found between the development of the virus (as shown by pathologic preparations) and titrations of the yolk sac for infectivity.

Non-pathogenicity of gonococci in larger animals. Ray E. Trussel and S. H. McNutt. *Proc. Soc. Exper. Biol. & Med.*, Utica, 46: 547-549, Apr. 1941.

Practically all common laboratory animals have been inoculated by natural and unnatural routes and the results have been almost uniformly discouraging. The data given here summarizes a series of attempts to infect 5 species of domestic animals by the inoculation of a pure culture of *Neisseria gonorrhoeae* intravaginally or into the conjunctival sac.

Three heifers, 5 female goats, 4 ewes, 2 sows, 1 mare, 2 bull calves and 1 bull were utilized as experimental animals. Inoculations were made by saturating sterile swabs with a freshly prepared saline suspension of a pure culture of *Neisseria gonorrhoeae* and inserting swabs deep into the vaginas of the female animals or beneath one lower eyelid. Cultures from the inoculated areas were made with sterile swabs every 2 to 3 days.

No gonococci were recovered from any of the inoculated animals. Each animal was observed for from 6 to 24 days. From seven cultures for each animal were made.

PUBLIC HEALTH ADMINISTRATION

Awards for tuberculosis and syphilis control programs. News item. *Rec.*, New York, 153: 331, May 7, 1941.

Two special contests were conducted by the United States Chamber of Commerce in cooperation with the American Public Health Association, in connection with the annual Inter-Chamber City Health Conservation Contest. These contests were for the most effective tuberculosis and syphilis control programs. Hartford, Connecticut, and Newton, Massachusetts received the award for the most effective tuberculosis control programs. Chicago, Louisville, Memphis, and Pasadena received the award for the most effective syphilis control programs.

ived the award for the most effective
philis control programs. The grading
mmittee consisted of a group of nation-
ly known health experts, with Dr. W. S.
ankin, of Charlotte, N. C., as chairman.

**ie high cost of neurosyphilis. Edi-
torial.** E. H. Lee. J. Nat. M. A., New
York, 33: 133-134, May 1941.

Neurosyphilis has been somewhat neg-
ted in the intensified drive against
philis. This is probably due to the fact
at it is comparatively noninfectious and
at, therefore, it is not a growing men-
e. But if looked at from the dollar-
d-cents point of view it is a serious
oblem. Approximate figures from one
the southern States show that there
e 6,000 Negro mental cases in its insti-
tions. Of these it is conservatively esti-
ated that 20 percent, or 1,200 patients,
ve neurosyphilis. At \$2.00 per day
r the care of each patient, over three-
urths of a million dollars of taxpayers'
oney would be spent in this one State
nually. For the 13 or 14 other States,
this rate, the cost of neurosyphilis
ould easily reach a total of about \$13-
0,000 annually, or nearly \$40,000,000
r a 3-year period. It is important, then,
at the problem of neurosyphilis be con-
sidered as an important part of syphilis
ontrol in general. In order to decrease
incidence adequate treatment of sys-
mic syphilis must be given, and no case
reated syphilis can be considered
red without an examination of the
inal fluid.

**rotection of soldiers, sailors, and work-
ers from syphilis and gonorrhea. II.
The citizen's part.** Rogers Deakin.
J. Social Hyg., New York, 27: 186-190,
Apr. 1941.

Not all the problems which have to do
th the treatment and control of syphilis
gonorrhea are purely medical in their
ture. Many factors enter into the re-
onse of an individual infected with a
nereal disease beside the reaction of
s blood or the rapidity with which his
ltures become negative. Research into
havior, attitudes, family relationships

and the many variables which combine to
influence an individual's actions play an
important part in the program to combat
the venereal diseases. Those persons who
are endeavoring to discover not only how
to find venereal disease patients but also
how to enlist the patients' active cooper-
ation are doing a work of inestimable
value.

In a certain clinic, before any attempt
at social control was made, just 2.5 per-
cent of patients with gonorrhea stayed
under treatment until cured. Since the
program was started which considered
the patient as a sick individual rather
than just another case, 75 percent of the
cases have been kept under observation
until cured.

Many citizens are busy in protecting
others from syphilis and gonorrhea. Phy-
sicians are devoting a large part of their
time to the study and teaching of these
diseases. The members of the Social Hy-
giene Association are expending much ef-
fort in fostering a clearer understanding,
and the country as a whole is not over-
looking the vital part that venereal dis-
eases play in the efficiency of a defense
program.

For obstetricians to ponder. Quart.
Bull. City of New York Depart. Health,
9: 30-32, May 1941.

A follow-up of birth certificates of the
past 9 months indicates that about 10 per-
cent of the pregnant women in New York
City reached the time of delivery without
having a blood test for syphilis during
pregnancy.

During the first quarter of 1941 the
total number of births was 27,122. On
25,733 of the birth certificates the sero-
logic test for syphilis of the mother was
reported as negative. Of the remaining
1,389 certificates, 222 reported a positive
test, while 1,167 failed to report any sero-
logic test. All of the 1,389 births were
investigated by medical epidemiologists,
and the results are shown in a table. It
is shown that 163 of the 222 cases with
positive reactions have a case report on
file; 34 are under treatment. Among the
reasons for no tests being done are given:

Negative, not reported, 46; positive, not reported, 3; no prenatal care, 847; emergency, 87; impossible to test, 8; patient refused, 64, of whom 47 were reported by private physicians.

It is felt that the reasons for not supplying information regarding the test for syphilis in the mother are most unsatisfactory. Even though the mother has not had prenatal care, the birth attendant should see that a specimen of the blood is taken at the time of delivery. With proper explanation of the value of the test to both the mother and the baby, it is difficult to believe that 47 out of 279 mothers delivered by private physicians would refuse to have the test performed. It also seems strange that 7 private physicians should report that they could not get into the vein.

Syphilis in pregnant women. Ella A. Macknight. M. J. Australia, Sydney, 1: 478-480, Apr. 19, 1941.

The results of routine Wassermann tests made on pregnant women attending the Queen Victoria Hospital, Melbourne, are given—series I covering from July 1, 1932, to November 25, 1936, and series II from July 1, 1937, to December 31, 1940. The procedure is to take blood for a Wassermann test on a patient's first visit to the antenatal clinic. In cases of emergency, as when the patient is admitted in labor, blood from the umbilical cord is used for the test. The number of such emergency cases, however, is very small; in series II in a total of 4,300 cases only 64 results were from the cord blood alone.

The general incidence of syphilis is low. In the total of 13,644 patients in both series, there were 133 with positive Wassermann reaction of whom 23 were considered as not syphilitic, which left 110 (0.8 percent) as probably syphilitic. None of the 23 patients considered as not syphilitic gave a history suggestive of syphilis nor showed any signs of syphilis. The 110 syphilitic cases include 3 of secondary, 71 of latent, and 4 of congenital syphilis, and 8 patients with a history of previous treatment, 4 under treatment at onset of pregnancy, and 20 on whom only

one positive reaction was obtained and no subsequent tests made.

From 63 treated patients (treatment of variable length—no details given) there were 59 live babies, and from 21 untreated patients 16 live babies. In series II there were 2 miscarriages among treated women and 1 (induced) miscarriage among the 4 untreated women. In both series there were 2 stillborn babies for the treated women, and 3 stillborn babies and 1 which lived a few hours for the untreated women.

Continuous treatment was used. If diagnosis was not made until the last months of pregnancy, concurrent weekly injections of novarsenobillon and bismuth were given; if the diagnosis was made earlier, overlapping novarsenobillon and bismuth courses were used.

Some effects of the law requiring premarital examinations. Illinois Health Messenger, Springfield, 13: 69, May 15, 1941.

In the 3½-year period up to December 31, 1940, 189,846 blood specimens have been tested under the premarital examination law in the laboratories of the Illinois Department of Public Health. That number, 2,615—or about 14 per 1,000—showed positive evidence of syphilitic infection. Since only about one-half of the specimens taken for this purpose are sent to the State laboratories, it is safe to presume that at least 5,000 cases of syphilis have been detected in the State because of the premarital examination law. It has been estimated that 15 to 20 percent of untreated cases of syphilis terminate in disorders of the nervous system and, therefore, a great many potential serious consequences have been prevented by the discovery of the 5,000 infected persons.

Since the adoption of the 1939 amendments to the law, 163 pregnant unmarried women have been granted the privilege of marriage in spite of evidence of infection with venereal disease in one or both of the parties. The woman was infected in 76 of these cases and the man in 8. Seventeen cases were infected with gonorrhea.

chea and 146 with syphilis. All but 6 of the 163 cases occurred in Cook County. Also since 1939 the privilege of marriage has been granted to 304 persons in whom the blood tests were positive but who, in the opinion of the physician, were no longer likely to spread the infection. The majority of these cases were also in Cook County, only 8 cases occurring downstate.

There were 162,259 tests done in the state diagnostic laboratories for gonorrhea in connection with the premarital examination. Of these, 967, or about 6 per 1,000, gave positive results. The volume of work done in the State laboratories has increased greatly. The number of blood tests for syphilis has increased from 46,968 in 1938 to 70,733 in 1940, and tests for gonorrhea from 36,337 in 1938 to 67,488 in 1940. The cost to the state, at the 1940 rate, is about \$40,000 per year.

The industrial clinic and its functions. A. G. Kammer. Fourth Saranac Laboratory Symposium on Silicosis, June 19-23, 1939. Pages 112-136.

An examining clinic for employees and applicants for employment was established by the Inland Steel Company at Indiana Harbor Works in January 1936, as part of a program to study plant health problems under the supervision of the Saranac Laboratory field staff. This industrial clinic was not in existence long before it became apparent that a great deal of consideration would have to be given to the subject of syphilis.

Each examinee was given a presumptive Kahn test. This test was too sensitive to be relied on entirely. Specimens showing a positive Kahn presumptive reaction were tested further by the Kahn standard, the two Kline, and the Eagle tests. Thus, three highly specific and two very sensitive tests were used.

Of 10,000 employees and applicants for employment tested consecutively, 482 (82 percent) had syphilis. Among employees tested, about 5 percent had syphilis; and among applicants for work, 4

percent had the disease. The disease was suspected from the histories given in 11 (2.28 percent) of the 482 cases. Physical findings indicating syphilis occurred 82 times (17.0 percent). The signs most frequently found were genital scars, changes in pupillary reflexes, widened aorta as determined by percussion and chest X-ray studies, and basal cardiac murmurs. There remained 389 (80.7 percent) who would have been missed if all examinees had not been subjected to the serologic tests.

Workers found to have syphilis were urged to report to their personal physicians for treatment. A letter of reference, listing the findings in the complete examination, was sent to the attending examining doctor or clinic in each case. The patients were recalled to the examining clinic every 3 months for the purpose of repeating all the serologic tests. Reports of the findings were mailed to the physicians treating the patients, and requests were made for statements of the amount of treatment given during the 3-month period. An attempt was made to have each worker with latent syphilis receive a total of 70 injections of neoarsphenamine and 70 injections of one or more heavy metals in an unbroken series. The opinion held by the clinic staff members is that the program is not a complete success. It is probably true that the treatment of syphilis in industrial workers should be given in free or part-pay municipal clinics.

In the discussion Kammer stated that for a few years all applicants for work at the Inland Steel Company who were found to have syphilis were rejected for employment. After a complete survey of all men already employed was made and it was found that the incidence of syphilis was not excessive and that the cases were amenable to treatment, selected applicants with syphilis were employed.

The Development of Public Health in Canada. Public health in Quebec. Elz. Pelletier. Canadian Public Health Association, Toronto, 1940, pp. 14, 17, 23.

Venereal diseases were made the subject of legislation in Quebec in 1865. By the Act 29, Victoria, c. 8, medical inspection of prostitutes was provided in Quebec, Lévis, Montreal, Sorel, Chambly, and in any other locality which the governor might designate. The law was to lapse after 5 years.

In 1920, the Provincial Government of Quebec having accepted the Canadian Federal Government's offer of \$47,388 a year for antivenereal disease work with the understanding that the Province would contribute an equal amount, the Division of Venereal Diseases was created, with laboratory facilities at Montreal and Quebec. These funds provided facilities throughout the province for the treatment of all cases and for an active program of public education through lectures and pamphlets. Because of the gradual decrease of the Canadian Government's subsidy and its discontinuance in 1931, the educational program was curtailed and the available funds utilized for new treatment centers. By 1931, 82 treatment centers had been provided for those who could not meet the expenses of treatment by their own physician and who could receive treatment free through the dispensary if they were temporarily unable to pay.

Valuable social data have been collected, indicating that the source of infection in 37 percent of the cases was from commercialized prostitution; from clandestine prostitution, 45 percent; congenital, unknown or accidental infections, 11 percent; and in marriage, 7 percent. The services of the provincial laboratory are free. In 1938, 224,278 treatments were given in the dispensaries with 106,483 injections, and a grand total of 145,228 blood tests and bacteriologic examinations were made in the provincial laboratories.

The Development of Public Health in Canada. Public health in Ontario.
J. T. Phair. Canadian Public Health Association, Toronto, 1940, pp. 82-83.

Following the report of a Royal Commission appointed to study the control of venereal diseases in Ontario, legislation was enacted in 1918 and a comprehensive program was undertaken. The need for a special division in the Provincial Board of Health was soon evident, and in 1920 the Venereal Disease Division was formed. In 1924 it was incorporated into the Division of Preventable Diseases, and in 1939 it was again made a separate division.

For the work of venereal disease control, \$115,000 was voted by the Province in 1920. Half of this sum was Ontario's share of \$200,000 granted by the Canadian Federal Government for venereal disease control. The Federal assistance was continued, although on a reduced basis, until 1932. Since that time an annual sum of \$102,000 has been made available for venereal disease control.

Nineteen clinics for the treatment of venereal diseases were established in the larger centers throughout the province and financed by the division. These clinics serve approximately 40 percent of the population of the province. For the remainder of the province, arrangements are made for the treatment of indigents by physicians under the supervision of the medical officer of health. A set schedule of fees has been adopted, and 75 percent of the cost is borne by the provincial health department. Further Federal assistance in the provision of arsenical drugs since 1938 has in part made possible this assistance to the municipalities without increase of appropriation. The clinics treat more than 10,000 cases of syphilis and gonorrhea each year.

Drop in disease rate traced to State control. San Francisco Examiner, May, 1941. California and West. Med., San Francisco, 54: 279, May 1941.

A decrease of 42.7 percent in the number of cases of early syphilis was reported to the California Medical Association by Merrill of the California State Department of Public Health on May 6, 1941.

Merrill attributed the decrease to the state's syphilis control program, now in its fifth year. He said that, of 98,789 men examined by doctors of California raft boards, 2,907 (2.95 percent) had positive tests.

He reported that premarital and selective service regulations have increased 300,000 yearly the number of tests made, with an annual discovery of 6,000 cases.

The Slossfield Health Center. An example of local medical service for mothers and children under public health auspices. Walter H. Maddux. *Am. J. Pub. Health*, New York, 31: 481-486, May 1941.

The Slossfield Health Center, a part of the Slossfield Community Center in Birmingham, Ala., was opened July 1, 1939, by the Jefferson County Board of Health with the cooperation of other agencies. Its function is to provide (for Negroes living in a specified area) maternity and child health service, a tuberculosis control program, and diagnostic and therapeutic care of persons with venereal diseases. It is estimated that 50,000 Negroes, approximately half of the Negro population of Birmingham, live within the area served by the center.

This is an outgrowth of the industrial health plan of the American Cast Iron Pipe Company, organized 18 years ago to serve the health needs of the workers and their families. About 2 years ago, the president of the company in cooperation with city and State authorities, developed a plan for the community center. The city of Birmingham gave a tract of land. The Works Projects Administration constructed buildings for the health and maternity clinics and for the educational and recreational activities. The National Youth Administration provided personnel for the educational and recreational activities. The Jefferson County Board of Health made provision for maternal and child health and venereal disease clinics. The Jefferson County Anti-

Tuberculosis Association and its Negro subsidiary, the Birmingham Health Association, made provision for tuberculosis control clinics. The Julius Rosenwald Fund provided funds to equip the health center and to train personnel. The Alabama Department of Public Health made available Social Security funds to pay physicians for clinic work and later additional maternal and child health funds to provide staff and equipment for the maternity clinic. The Children's Bureau loaned a Negro pediatrician from its staff to be medical director of the health center. Financial aid for many "extras" has come from a local community chest supported by Negroes of the area.

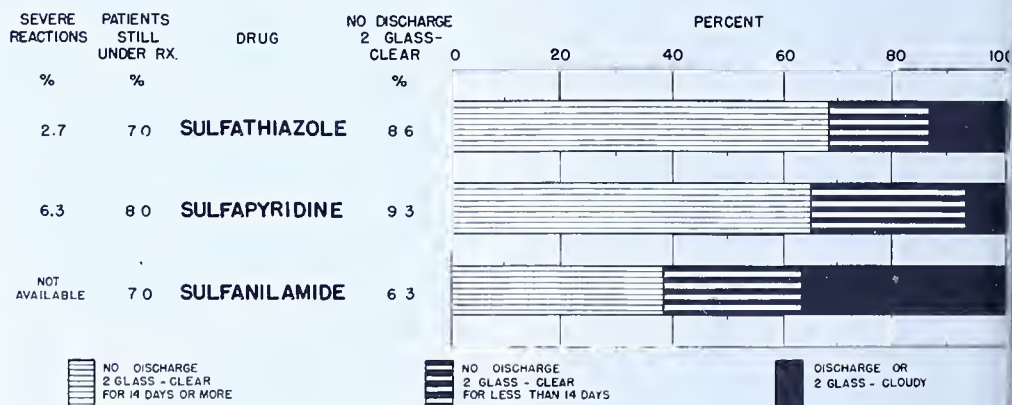
In 1937, the area now served by the center had but one clinic period for prenatal service and one for child health each week. A syphilis clinic was opened in January 1939. After the health center opened, 21 weekly clinic periods were provided. Legal residence in the area and inability to pay for private medical services are the requirements for admission to the center as established by the Jefferson County Board of Health.

The medical staff consists of the full-time medical director (a pediatrician), 4 senior medical consultants (white physicians), 8 Negro clinicians paid 5 dollars per 2-hour clinic period (venereal disease or maternal and child health) by the Jefferson County Board of Health. In addition, there are 29 other Negro employees, including one junior obstetric consultant, one dentist, a medical social worker, a resident supervisory nurse, 6 public health nurses scheduled to assist at clinics as part of their general community services, and a clerk. The rest of the staff is supplied by the Work Projects Administration and the National Youth Administration.

The medical clinic is diagnostic and serves primarily to discover cases of syphilis. Patients found to be nonsyphilitic but who need treatment for other conditions are referred elsewhere.

RAPID APPRAISAL OF SULFONAMIDE DRUGS IN THE TREATMENT OF GONORRHEA IN THE MALE MONTHLY REPORT

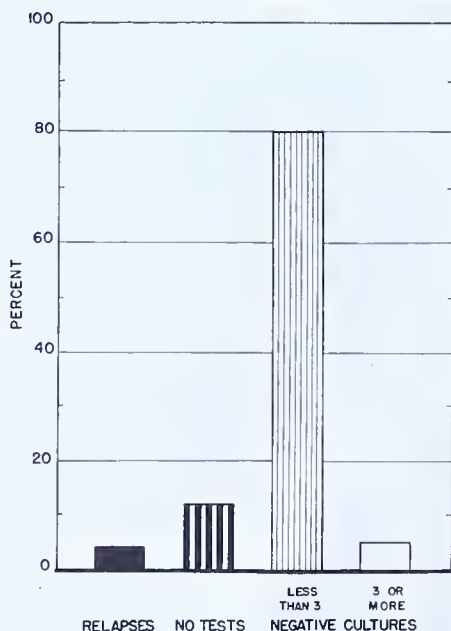
DISAPPEARANCE OF SYMPTOMS BY END OF FOURTH WEEK OF OBSERVATION



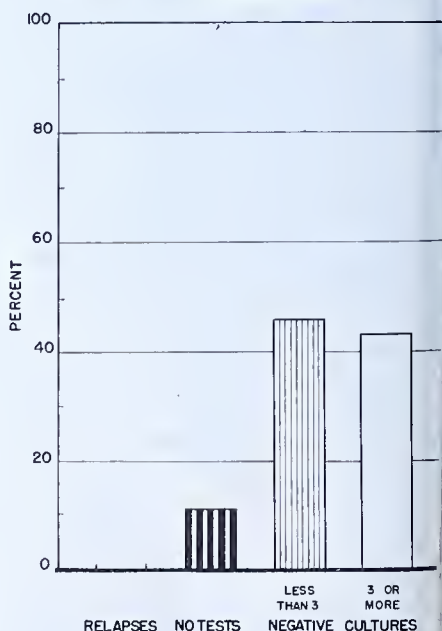
SULFATHIAZOLE

LABORATORY FOLLOW-UP IN INDICATED PERIODS ON PATIENTS SHOWING NO DISCHARGE AND CLEAR 2 GLASS TEST FOR 14 DAYS

STATUS AFTER TWO WEEKS FOLLOW-UP



STATUS AFTER THREE WEEKS FOLLOW-UP



NEW DRUGS

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Analysis of 532 Cases of Interstitial Keratitis with Particular Reference to Standardization Treatment

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and

ELEANOR VANDOREN

INTERSTITIAL keratitis is a well-known cause of impaired vision or blindness. Its importance may be seen from a previous study by the Cooperative Clinical Group (1) which showed that interstitial keratitis is the most frequent disabling complication of congenital syphilis. This complication was found in approximately one-third of 1,010 cases studied.

Material studied.—The present study comprises an analysis of 532 case records of patients with interstitial keratitis who were treated or observed for at least a year. All of the patients had congenital syphilis. Although other aspects of interstitial keratitis are considered, the study is particularly concerned with the evaluation of various plans of antisyphilitic treatment in terms of visual acuity of the patient at final examination.¹

Material for this study was made available by the syphilis clinics of the Western Reserve University, the Johns Hopkins University, the Mayo Clinic, the University of Pennsylvania, and the Wills Eye Hospital, through the Cooperative Clinical Group, including Harold N. Cole, M. D., Joseph Earle Moore, M. D., Phil A. O'Leary, M. D., John H. Stokes, M. D., Joseph V. Klauder, M. D., for the Cooperating Clinics, and Thomas Parran, M. D., R. A. Vanderlehr, M. D., Lida J. Usilton, M. A., and Eleanor Vandoren, representing the U. S. Public Health Service.

This investigation was supported by a grant from the John and Mary R. Markle Foundation.

Impairment of visual acuity is caused by changes in the cornea which are the direct result of interstitial keratitis. These corneal changes include opacities, deep blood vessels, folds in Descemet's membrane, precipitates, corneal dystrophy, and changes in the curva-

Visual acuity was determined in some patients with refraction and in other patients without refraction. It is apparent from chart 1 (particularly in patients whose interstitial keratitis was inactive) that in the majority of patients with uncorrected visual acuity, refraction was not performed either because visual acuity was so good that refraction was unnecessary or because visual acuity was so poor that refraction would have been of limited value. Apparently, then, a false picture of the efficacy of treatment would have been obtained if the study had been limited to patients with corrected visual acuity.

Control group.—An ideal control group would consist of a random sample of previously untreated patients with acute interstitial keratitis who were observed a year or more subsequent to admission but not treated. Since this was not possible, an alternative was suggested for obtaining an indication of visual acuity resulting in untreated interstitial keratitis. This was to select patients with bilateral inactive interstitial keratitis of

ture of the cornea which cause refractive errors. Other causes may be iridocyclitis, glaucoma, cataract, and chorioretinitis. Impairment of visual acuity therefore may not necessarily connote a failure of antisyphilitic treatment. A more accurate evaluation of the results of such treatment is not visual acuity alone, but a correlation of visual acuity with and without refraction and with results of slit-lamp and ophthalmoscopic examinations. Patients with interstitial keratitis who also had cataract, glaucoma, primary or secondary optic atrophy were excluded from that part of the study concerned with evaluation of treatment.

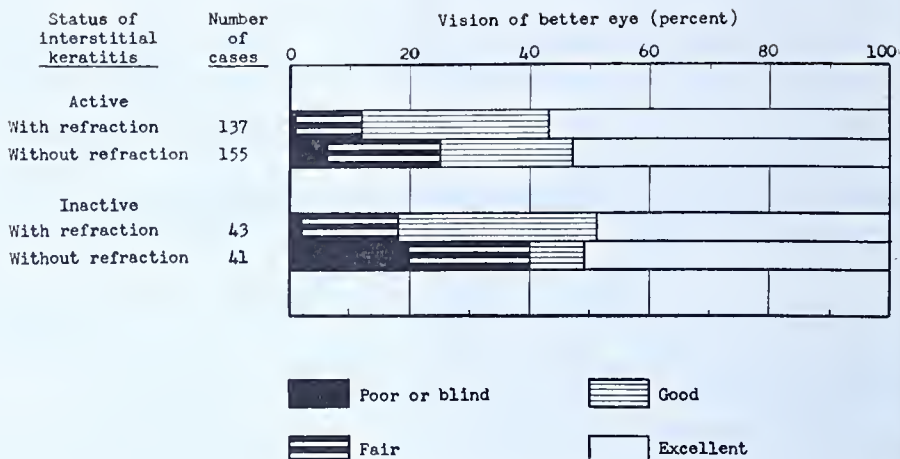


CHART 1.—Final vision of patients with active and inactive interstitial keratitis, determined with and without refraction.

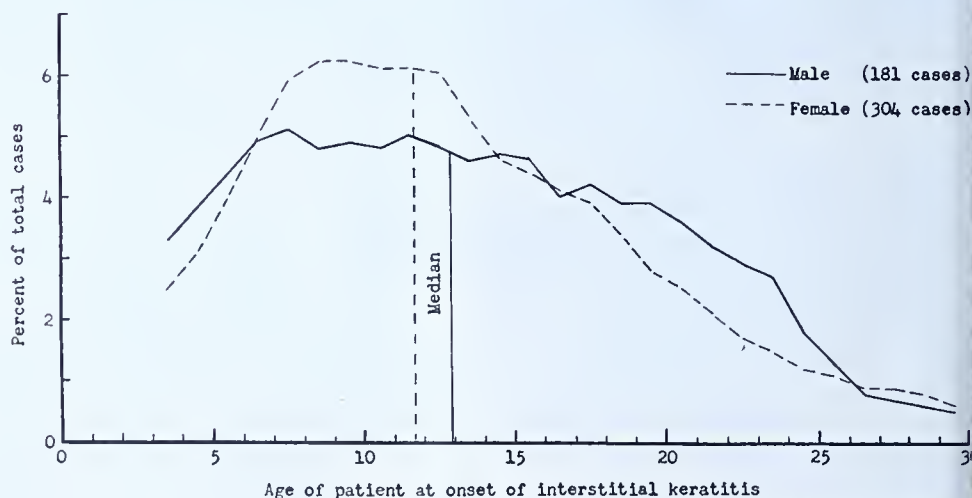


CHART 2.—Distribution of patients with interstitial keratitis by age at onset.

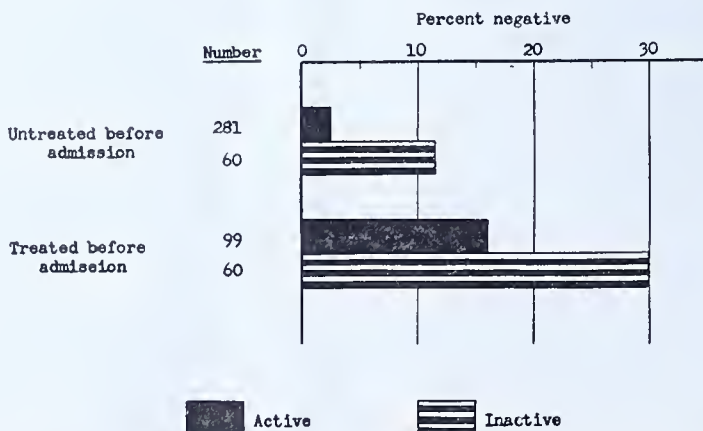


CHART 3.—Percentage of negative blood reactions in treated and untreated patients by status of interstitial keratitis on admission.

least a year's duration who had received little or no treatment. The control group thus devised consists of 87 patients, none of whom had received more than a total of six injections of an antivenereal, heavy metal, or both. Visual acuity was determined with refraction of 7 percent and without refraction in 17 percent. In the remaining 16 percent there were no refraction data.

Incidence of race, sex, and age.—Fifty-three percent of the patients were white, and 27 percent were Negroes. In statistical studies of interstitial keratitis show a greater incidence in males. In this study approximately 60 percent of the patients in each of the cooperating clinics were females.

Chart 2 shows the age curves and the median age at onset of interstitial keratitis for 181 male and 304 female patients. In the females interstitial keratitis developed with the greatest frequency between the seventh and thirteenth years, with 12 years as the median age at onset. In the males, although there was a slightly downward trend from about the tenth year, interstitial keratitis developed at a fairly constant rate from the tenth to the twentieth year. Of the 485 patients for whom the age at onset was known, 13 developed interstitial keratitis before the age of 3 and 8 after the age of 10.

Serologic reaction.—The two factors which appear to have the greatest influence on the serologic reaction of the patient are previous treatment and status of interstitial keratitis. As will be seen in chart 3, patients with inactive interstitial keratitis, who had been treated, had the highest percentage of negative reactions (30 percent); the smallest number of negative reactions was observed in untreated patients with active interstitial keratitis (2.5 percent). In the untreated group the inactive patients were found to be negative more than four times as frequently as the active patients (11.7 percent to 2.5 percent).

Age of the patient and duration of interstitial keratitis also appeared to be influencing factors, but the higher per-

centage of positive reactions in the younger age groups and shorter duration periods seem to be accounted for by the preponderance of active cases in these groups.

Serologic reaction after treatment.—The difference in the percentage of patients who had reversal of serologic reactions following different amounts of treatment was not great. A difference, however, was noted in the different age groups. Forty-six percent had reversal of serologic reactions to negative in the age group 0 to 9 years, compared with 22 percent in the age group 10 to 19 and 17 percent in the age group 20 to 29 years.

Incidence of other syphilitic manifestations.—Table 1 shows the relative frequency with which concomitant syphilitic manifestations occurred in 532 patients. Those most frequently observed were as follows: Hutchinsonian teeth, 40 percent; bone and joint involvement (as enumerated in table), 35 percent; labyrinthine disease, 10 percent; chorioretinitis,² 8 percent; and neurosyphilis (symptomatic and asymptomatic), 8 percent.

Bone and joint involvement and also neurosyphilis were observed with greater frequency in the males than in the females. Bone and joint involvement,

²Chorioretinitis was not separated into the different types as classified by Sidler-Huguenin (Beitr. z. Augenheilh., 6: 1904). These four types characteristically involve the periphery of the fundi and appear early in congenital syphilis, invariably antedating interstitial keratitis. Chorioretinitis, on the other hand, may appear with interstitial keratitis associated with uveitis. The incidence of chorioretinitis in patients with interstitial keratitis as reported by different writers varies considerably. Dalsgaard-Nielsen gives the incidence as 16 percent (Acta Ophth., 17: 43, 1939); Derby, as 55 percent (Ophth. Rec., 26: 563, 1917); Cunningham, as 68 percent (Tr. Ophth. Soc. of the United Kingdom, 42: 44, 1922); Spicer, as 29 percent (Brit. J. Ophth., Monograph Supp. I, 1924); Igersheimer, as 36 percent (Syphilis und Auge, Springer, Berlin, 1928, 2d ed.). Ophthalmoscopic examination to demonstrate old chorioretinitis in the periphery of the fundi and slit-lamp microscopy to demonstrate sequelae of interstitial keratitis are valuable aids in the diagnosis of congenital syphilis at any age.

TABLE 1.—*Tabulation of cases of interstitial keratitis showing incidence of associated syphilitic involvements by race and sex*

Associated syphilitic involvements	White						Colored						Total					
	Male		Fe-male		Total		Male		Fe-male		Total		Male		Fe-male		Total	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Teeth	61	41.8	98	40.3	159	40.9	18	34.6	36	39.6	54	37.8	79	39.9	134	40.1	213	40.0
Bone and joint disease	68	44.6	81	33.3	149	38.3	18	34.6	21	23.1	39	27.3	86	43.4	102	30.5	188	36.9
Fournier's tibia	38	26.0	39	16.0	77	19.8	7	13.5	4	4.4	11	7.7	45	22.7	43	12.9	88	16.8
Clutton's joints	13	8.9	19	7.8	32	8.2	9	17.3	9	9.9	18	12.6	22	11.1	28	8.4	50	9.5
Prominent frontal bossae	14	9.6	16	6.6	30	7.7	1	1.9	3	3.3	4	2.8	15	7.6	19	5.7	34	6.4
Saddle nose	10	6.8	8	3.3	18	4.6	1	1.9	2	2.2	3	2.1	11	5.6	10	3.0	21	4.0
Other and unspecified	9	6.2	18	7.4	27	6.9	3	5.8	4	4.4	7	4.9	12	6.1	22	6.6	34	6.4
Labyrinthine disease	10	6.8	22	9.1	32	8.2	4	7.7	17	18.7	21	14.7	14	7.1	39	11.7	53	10.1
Chorioretinitis	11	7.5	27	11.1	38	9.8	—	—	4	4.4	4	2.8	11	5.6	31	9.3	42	8.0
Central nervous system	20	13.7	15	6.2	35	9.0	3	5.8	3	3.3	6	4.2	23	11.6	18	5.4	41	7.8
Asymptomatic	9	6.2	8	3.3	17	4.4	3	5.8	2	2.2	5	3.5	12	6.1	10	3.0	22	4.2
Symptomatic (— CSF ¹)	7	4.8	3	1.2	10	2.6	—	—	1	1.1	1	.7	7	3.5	4	1.2	11	2.1
Symptomatic (+ CSF)	4	2.7	4	1.6	8	2.1	—	—	—	—	—	—	4	2.0	4	1.2	8	1.5
Skin and mucous membrane	5	3.4	13	5.3	18	4.6	1	1.9	4	4.4	5	3.5	6	3.0	17	5.1	23	4.4
Visceral disease	6	4.1	8	3.3	14	3.6	1	1.9	1	1.1	2	1.4	7	3.5	9	2.7	16	3.0
Cranial nerves (except VIIIth)	1	.7	4	1.6	5	1.3	—	—	1	1.1	1	.7	1	.5	5	1.5	6	1.1
None	35	24.0	82	33.7	117	30.1	16	30.8	33	36.3	49	34.3	51	25.8	115	34.4	166	31.5
More than one	48	32.9	76	31.3	124	31.9	9	17.3	20	22.0	29	20.3	57	28.8	96	28.7	153	28.9
Total cases	146		243		389		52		91		143		198		334		532	

¹ Cerebrospinal fluid.

chorioretinitis, and symptomatic neurosyphilis were more common in the white than in the Negro patients. The difference in chorioretinitis may be explained by the fact that the fundi were examined in 50 percent of the white patients and in 30 percent of the Negro patients. The observation of a greater incidence of bone and joint involvement, of chorioretinitis, and of symptomatic neurosyphilis is consistent, however, with the Cooperative Clinical Group study of late congenital syphilis (1) in which it was observed that congenital syphilis ran a stormier course in the white than in the Negro patient.

Eighth nerve involvement, long associated with interstitial keratitis since Hutchinson included it in his well-known triad, was present in 10 percent of the 532 patients in this study, but in only 6 percent of the 1,010 patients comprising the congenital syphilis group (1).

Neurosyphilis, both symptomatic and asymptomatic, was observed less frequently (8 percent) than in the entire congenital syphilis group (14 percent).

Of the patients with asymptomatic neurosyphilis, the majority showed the group II type³ of spinal fluid. The spinal fluid was negative in the majority of patients in the symptomatic group. In this latter group vascular neurosyphilis and tabes were the two principal diagnoses. There was one patient with paresis and one patient with taboparesis, both of whom had group III spinal fluid. Igersheim (2) mentioned the rarity of either primary optic atrophy or ocular motor paralysis in association with interstitial keratitis. Kopp and Solomon stressed the relative infrequency of

³ Group II (moderate)—Cases in which cell count and globulin content are increased, the Wassermann test is positive or weakly positive, and colloidal tests are indeterminate or positive—if the latter, they are usually of the syphilitic zone type.

Group III (severe)—Cases in which spinal fluid shows the so-called paretic form, i. e., marked excess of globulin, strongly positive Wassermann (0.2 cc. or less) and a paretic type of colloidal curves. The cell count is above normal and contains in addition to small lymphocytes, large lymphocytes and polymorphonuclear leukocytes.

stitial keratitis as a concomitant of genital neurosyphilis, especially juvenile paresis. In this regard it is to be noted that only 0.4 percent of the patients in this series had paresis or taboparesis, compared with 4.6 percent in the entire genital syphilis group (1).

Status and duration of interstitial keratitis.—The status of interstitial keratitis in 532 patients on admission was as follows:

	Num- ber	Per- cent
Unilateral—Active ⁴ -----	151	28.4
Inactive ⁴ -----	17	3.2
Bilateral—Active, one eye -----	28	5.3
Active, both eyes -----	223	41.9
Inactive, both eyes -----	113	21.2

The duration on admission was less than 3 months in 89 percent of 151 patients with active unilateral interstitial keratitis; it was less than 2 weeks in 13 percent, 2 to 6 weeks in 57 percent, and more than 6 weeks in the rest.

In 60 percent of 223 patients with active bilateral interstitial keratitis the duration was less than 3 months. Of this group the duration ranged from 1 to 6 weeks in 34 percent. In 15 percent the duration was more than a year. No distinction was made between first attack of interstitial keratitis and recurrence. This accounts for the fairly high percentage of patients with active interstitial keratitis of more than 1 year's duration.

*Treatment employed in study.*⁵—ROUSE. This consisted of an arsenical in conjunction with a heavy metal. Among the arsenicals employed, neoarsphenamine and old arsphenamine predominated.

As used in this paper the term "active" refers to the presence, in a variable degree, of the following symptoms of inflammation: corneal congestion, increased lacrimation, photophobia, and evidence of uveitis. Associated with these symptoms the cornea is hazy and opacities are present. The term "inactive" refers to the absence of these symptoms. In the early stage there are corneal opacities or the media is clear on gross examination. These patients were treated prior to clinical experimentation with riboflavin in interstitial keratitis.

In the order of decreasing frequency of their use, the other arsenicals employed were silver arsphenamine, sulfarsphenamine, mapharsen, bismarsen, and tryparsamide. The heavy metals used were bismuth subsalicylate and mercury.

Of the 532 patients, 97 percent were treated with an arsenical, practically all in conjunction with a heavy metal. Bismuth was more popular than mercury. Active cases, in which the final visual acuity was tabulated by amount of treatment, received a median of 28 injections of an arsenical and 51 injections of a heavy metal (or weeks of mercury injections); inactive cases, a median of 21 injections of an arsenical and 44 injections of a heavy metal. One-fourth of the active cases received as much as 80 injections of either bismuth or mercury, and only 7 percent received less than 20 injections of a heavy metal and less than 20 injections of an arsenical.

IODIDES. Among the 290 patients receiving iodides, oral administration of potassium iodide predominated. The dosage ranged from 30 to 270 grains daily. Sixteen patients were treated with sodium iodide intravenously, in doses of from 2 to 10 grains per injection. The total number of injections varied from 3 to 31.

FEVER THERAPY. This embraced induced malaria with an average of 10 fever bouts, mechanically induced fever with an average of 8 to 9 bouts of 4 to 5 hours, intramuscular injections of sterile milk, and intravenous injections of vaccine—typhoid, antigen H,⁶ and pyrifur.⁷ Typhoid vaccine was the most common fever producing agent used in the treatment of the 127 patients who were given fever therapy.

LOCAL HEAT THERAPY. The thermophore⁸ was employed in one clinic in an

⁶ Antigen H is the flagellated portion of the typhoid bacillus.

⁷ Pyrifur is a Swiss preparation made from the colon bacillus.

⁸ The thermophore is an instrument employed by ophthalmologists for heat therapy of pathologic lesions in the cornea. After local anesthesia, the thermophore was applied to the cornea for 1 minute, at variable tem-

endeavor to heat the cornea to the thermal death point of *Spirochaeta pallida*. The uninvolved eye was treated in the hope of preventing involvement; the involved eye, in order to determine if heat locally applied was of benefit in treatment of interstitial keratitis. After clinical use and after experimental studies,⁹ it was apparent that these purposes were not achieved. The use of the thermophore in the treatment of interstitial keratitis was, therefore, discontinued.

Interval between first and second eye involvement.—An attempt was made to ascertain from the material the influence of treatment in preventing progression of unilateral interstitial keratitis to the second eye.¹⁰ It was impossible to determine the effect of treatment subsequent to admission largely because of the short interval elapsing between first and second eye involvement in the majority of cases. A reduction in the probability of second eye involvement, although not a significant one, was found among cases which had had previous treatment.

With reference to the axiom that interstitial keratitis inevitably becomes bilateral (4), it appeared that *the chance of escaping bilateral involvement increases in direct ratio to the lapse of time*

peratures ranging from 120° F. (48.9° C.) to 128° F. (53.3° C.), three times weekly for 12 to 15 consecutive treatments.

⁹The measurement of the degree of penetration of heat applied to the anterior surface of the cornea of rabbits; the maximum temperature the cornea of man can tolerate with safety; the time required to kill *Spirochaeta pallida* when heated to 120° F. (48.9° C.) are discussed in "Clinical and experimental studies of interstitial keratitis," by J. V. Klauder, E. R. Gross, and H. F. Robertson, *J. Invest. Dermat.*, 2: 157-173, 1939.

¹⁰There are several theories of the mechanism that motivates the onset of interstitial keratitis and the involvement of the second eye. The simplest explanation of second eye involvement is that it is an expression of elective or paired organ sensitization. This concept envisages similar organs with a common trophonervous influence as a closed entity with a common inflammatory reaction. This concept could also serve to explain other paired organ involvement in congenital syphilis—deafness and symmetrical serous synovitis.

from the onset of interstitial keratitis in the first eye. This may be seen in table 2, which shows the intervals between involvement of the first and second eye in treated and untreated patients for whom this information was available, either through clinical observation or from the patient's statement. Of the 355 patients observed for 2 years, 42 percent experienced a second eye involvement within 1 month after the first, and in 29 percent more the condition became bilateral at intervals ranging up to 2 years. In the cases observed 10 years or more, only 8 percent more had progressed to bilateral involvement. This left 21 percent who had remained unilateral for more than 10 years.

TABLE 2.—Percentage of patients in whom the interstitial keratitis had become bilateral by the indicated time after involvement of the first eye.

Length of time	Total cases observed	Bilateral	
		Number	Percent
1 month.....	355	149	42.0
2 months.....	355	182	51.3
3 months.....	355	193	54.4
4 months.....	355	206	58.0
5 months.....	355	210	59.2
6 months.....	355	215	60.6
1 year.....	355	237	66.8
2 years.....	355	252	71.0
3 years.....	313	227	72.5
4 years.....	245	176	71.8
5 years.....	211	153	72.5
10 years.....	172	135	78.5
Over 10 years.....	67	53	79.1

A study confined to 151 cases, diagnosed on admission as active and unilateral, supported the above finding. The interstitial keratitis remained unilateral throughout observation (1 year or more) in 33 percent of the cases of less than 1 month's duration compared to 51 percent when the duration was 1 to 2 months.

Of the 151 cases, 96 had had no previous treatment. Investigation of the 6 showed that the increased chance from the first to the second month of escaping second eye involvement was not due to treatment. Among the untreated cases of less than 1 month's duration, 28 percent remained unilateral compared to 50 per-

ent among untreated cases of 1 to 2 months' duration.

The relation of the active stage of interstitial keratitis to the chance of second eye involvement was determined by comparing the 151 cases with 17 which were unilateral but inactive on admission. The majority in both groups had been untreated previous to admission, but all were treated subsequent to admission. Seventy-one percent of the inactive cases remained unilateral compared to only 40 percent of those active on admission.

Effect of routine treatment on visual acuity.—Visual acuity is interpreted in this discussion as follows:

Excellent	6/6 (20/20)
	6/9 (20/30)
Good	6/12 (20/40)
	6/15 (20/50)
Fair (practical)	6/21 (20/70)
	6/30 (20/100)
	6/60 (20/200)
Poor	Less than 6/60 (20/200)
Blind	Hand movements, light perception, and inability of patient to go about unattended.

The visual acuity on admission and on final examination of 271 eyes of patients treated in the active stage of interstitial keratitis and of 115 eyes of patients treated in the inactive stage is shown in chart 4. It appears that *treatment administered in the inactive stage of interstitial keratitis is of limited value in improving visual acuity.* The visual acuity on admission was poor or nil in 55 percent of eyes of patients treated in the inactive stage of interstitial keratitis compared with 22 percent on final examination. On the other hand the visual acuity on admission was poor or nil in 55 percent of eyes of patients treated in the active stage of the disease compared with 11 percent on final examination. The improvement of visual acuity represented in the difference between 55 and 44 percent cannot be credited entirely to the effect of treatment, since after the

subsidence of acute inflammatory symptoms of interstitial keratitis, in the absence of treatment, improvement of visual acuity occurs.

ACTIVE INTERSTITIAL KERATITIS. Chart 5 stresses the value of treating active cases with 20 or more arsenical injections plus heavy metal. It is shown that in 183 eyes of patients treated with "20 or more" visual acuity was excellent in 37 percent of eyes on final examination, compared with 27 percent of 88 eyes of patients treated with "less than 20." Additional evidence is the fact that in patients treated with "more than 20" the

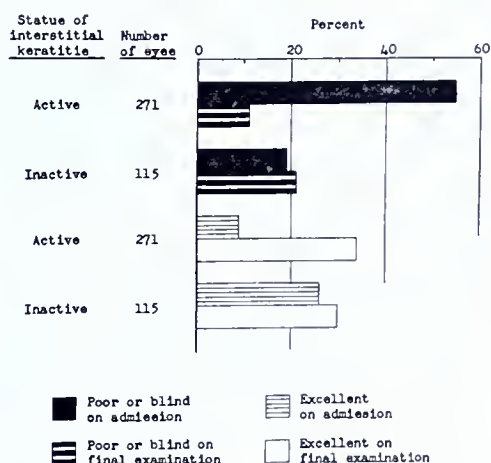


CHART 4.—Comparison of visual acuity on admission with final visual acuity of patients with active and patients with inactive interstitial keratitis.

percentage of eyes with excellent visual acuity on admission was 7, which increased to 37, a difference of 30 percent; whereas, in patients treated with "less than 20," the increase was from 14 to 27, a difference of 13 percent.

Among the patients receiving this minimum treatment 57 percent of 183 eyes had poor visual acuity on admission compared with 9 percent on final examination, a difference of 48 percent. Among patients treated with less than this amount, 50 percent of 88 eyes had poor visual acuity on admission compared with 14 percent on final examination, a difference of 36 percent.

The importance of employing at least 20 injections of an arsenical with interim

heavy metal in treatment of interstitial keratitis in the active stage is emphasized once more. This phase in therapy of the disease was stressed in the Cooperative Clinical Group's study (1).

INACTIVE INTERSTITIAL KERATITIS. Chart 6 is made from a series of patients with inactive interstitial keratitis. The visual acuity of these patients on admission, calculated on a total of 115 eyes, was excellent in 26 percent. The chart shows

Consistent with the conclusion drawn from chart 4, it further appears that treatment administered in the inactive stage of interstitial keratitis is of limited value in improving visual acuity. This seemed to apply whether the patient had or had not, received treatment prior to the time the interstitial keratitis became inactive. *The importance of diagnosis and treatment of interstitial keratitis while still active is apparent.*

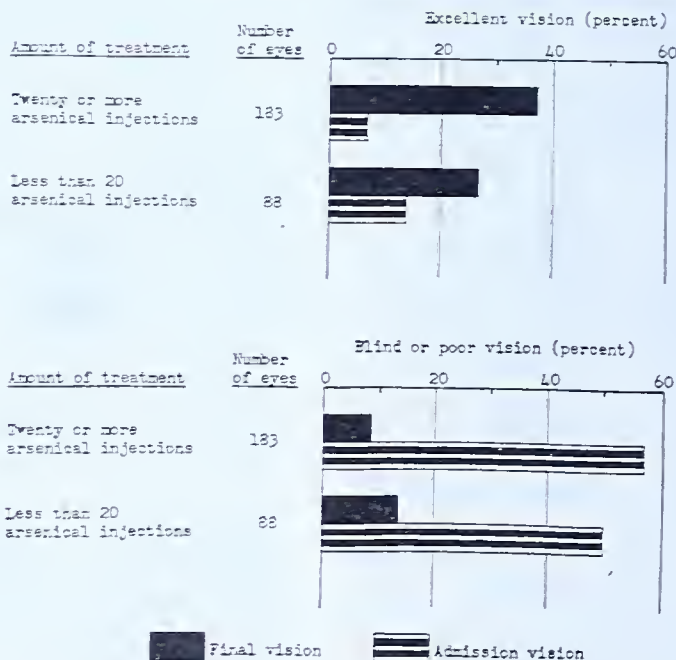


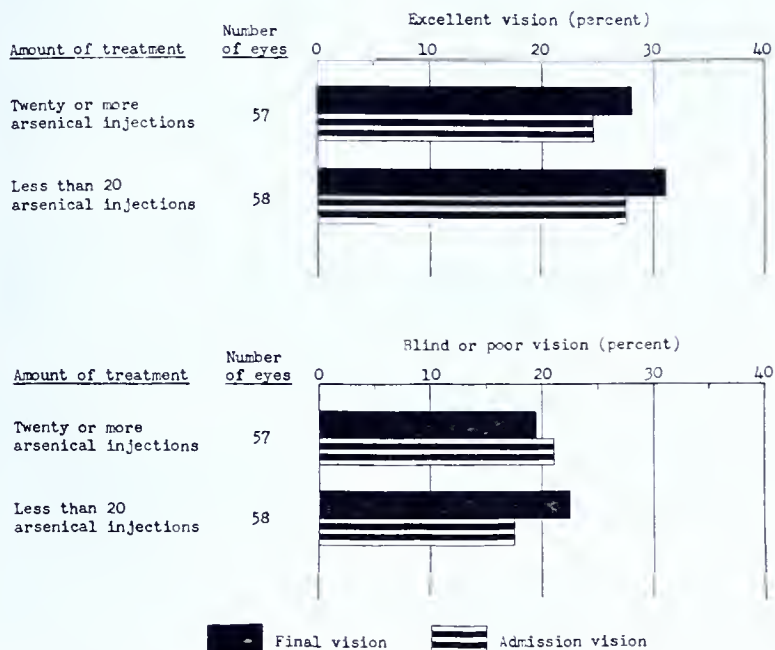
CHART 5.—Comparative value of different amounts of arsenical treatment of patients with active interstitial keratitis.

the influence of 20 or more arsenical injections (plus heavy metal) and of "less than 20" on the visual acuity of patients at final examination. The increase in excellent vision was the same for patients treated with the smaller and the larger amounts. The change in both groups was slight (3.5 percent) and probably due to visual refraction rather than to treatment. "More than 20" caused a 1.5 percent decrease in the percentage of eyes with poor visual acuity or blindness after treatment compared with the percentage before treatment. With "less than 20" there was an increase of 5 percent in the percentage of eyes with poor visual acuity or blindness compared with the percentage before treatment.

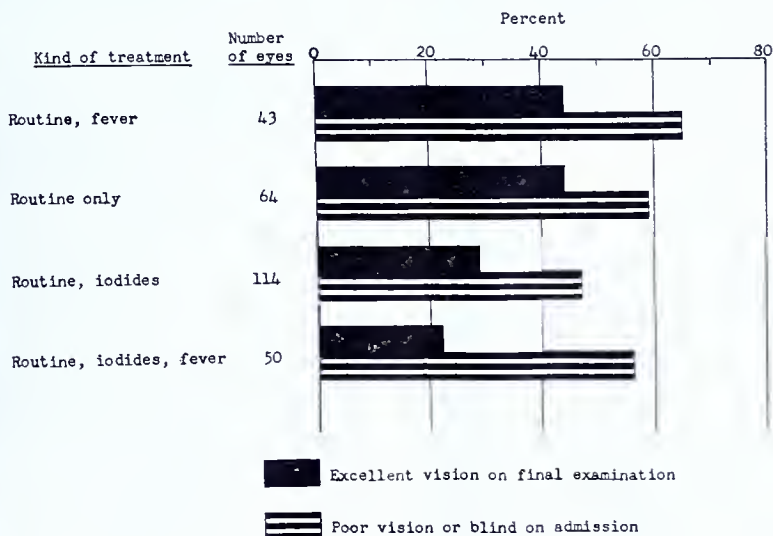
Effect of fever and of iodides in treatment of interstitial keratitis.—ACTIVE STAGE. In chart 7 (which includes on those patients with both an admission and final visual acuity examination) comparison is made of the effectiveness of different plans of therapy in treatment of patients with interstitial keratitis in the active stage. This chart is based on a total of 271 eyes. The percentage of eyes of patients with poor visual acuity or blindness on admission is compared with the percentage having excellent visual acuity on final examination, following different plans of therapy. Best results were obtained in patients receiving routine treatment only and routine treatment plus fever therapy. Forty-four per

nt of the eyes of patients receiving these
 70 eyes of treatment had excellent visual
 acuity on final examination. The per-
 centage of eyes with poor visual acuity

The percentage of eyes with excellent
 visual acuity on final examination follow-
 ing routine treatment with the addition
 of iodides was 29; following routine treat-



ART 6.—Comparative value of different amounts of arsenical treatment of patients with inactive interstitial keratitis.



ART 7.—Comparative value of different plans of treatment of patients with active interstitial keratitis.

more treatment was greater in patients
 receiving routine treatment plus fever
 than in patients who were treated with
 any one of the other plans of therapy.

ment with the addition of iodides and
 fever therapy the percentage was 22.
 These poor results cannot be attributed
 to "last resort" treatment, since the latter

two plans of therapy were undertaken as a matter of choice in the majority of cases.

Chart 8 and table 3 (based on patients with a final visual acuity examination) show the percentage of eyes with excellent visual acuity on final examination, as well as the percentage with good, fair, and poor visual acuity, following different

plans of therapy. Visual acuity of treated patients comprising the con group is also shown. Fifty-one perc of the eyes of patients given rou treatment plus fever therapy had ex lent visual acuity on final examinat and 18 percent had good visual acu The percentage having excellent vis acuity was significantly greater than t

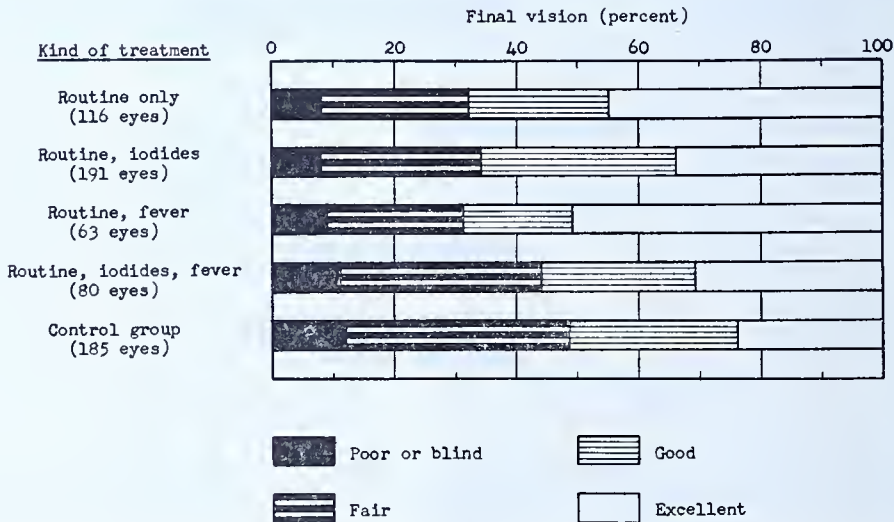


CHART 8.—Final visual acuity of patients with active interstitial keratitis following different plans of treatment compared with visual acuity of control group.

TABLE 3.—Visual acuity after various kinds of therapy compared with visual acuity of control group (based on total eyes)

Visual acuity	Control cases		Active on beginning treatment										Inactive on beginning treatment				
			Routine only		Routine and fever		Routine and iodides		Routine, iodides, and fever		Total		Routine only		Routine and iodides		Total
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number
6/6	22	11.9	33	28.4	20	31.7	34	17.8	12	15.0	99	22.0	15	23.8	15	14.3	30
6/9	23	12.4	19	16.4	12	19.0	31	16.2	13	16.3	75	16.7	11	17.5	16	15.2	27
6/12	24	13.0	13	11.2	3	4.8	27	14.1	8	10.0	51	11.3	5	7.9	9	8.6	14
6/15	26	14.1	14	12.1	8	12.7	35	18.3	12	15.0	69	15.3	9	14.3	14	13.3	23
6/21	18	9.7	13	11.2	7	11.1	20	10.5	10	12.5	50	11.1	2	3.2	10	9.5	12
6/30	29	15.7	9	7.8	5	7.9	10	5.2	7	8.8	31	6.9	1	1.6	9	8.6	10
6/60	21	11.4	6	5.2	2	3.2	19	9.9	9	11.3	36	8.0	7	11.1	9	8.6	16
—6/60	16	8.6	6	5.2	4	6.3	11	5.8	4	5.0	25	5.6	5	7.9	13	12.4	18
Blind	6	3.2	3	2.6	2	3.2	4	2.1	5	6.3	14	3.1	8	12.7	10	9.5	18
Total	185	100.0	116	100.0	63	100.0	191	100.0	80	100.0	450	100.0	63	100.0	105	100.0	168
Excellent	45	24.3	52	44.8	32	50.8	65	34.0	25	31.3	174	38.7	26	41.3	31	29.5	57
Good	50	27.0	27	23.3	11	17.4	62	32.5	20	25.0	120	26.7	14	22.2	23	21.9	37
Fair	68	36.8	28	24.1	14	22.2	49	25.7	26	32.5	117	26.0	10	15.9	28	26.7	38
Poor or blind	22	11.9	9	7.8	6	9.5	15	7.9	9	11.3	39	8.7	13	20.6	23	21.9	36

ained with routine treatment plus i-
les or routine treatment plus iodides
1 fever therapy. The percentage of
es with excellent visual acuity on final
amination following routine treatment
y was 44; following routine treatment
h the addition of iodides, 34; and fol-
wing routine treatment with the addi-
n of iodides and fever therapy, 31.

Comparison of the best treated group
outine plus fever therapy) with the con-
l group, as shown in chart 8, discloses
following percentage distribution in
al visual acuity:

	Excel- lent	Good	Fair	Poor or blind
Best treated group—	51	17	23	10
Untreated group—	24	27	37	12

The greatest variation in the proportion
patients with poor visual acuity follow-
the different plans of treatment was
y from 8 to 11 percent. Apparently
n, *the superiority of one plan over
other involves an increase in the pro-
tion of patients with excellent vision
following treatment and not a decrease in
proportion whose sight remained poor.*

INACTIVE STAGE. The data in this study
not indicate that iodides were benefi-
In the treatment of inactive intersti-
keratitis. Of 34 eyes of patients with
active interstitial keratitis who were
en routine treatment but no iodides, 21
cent had excellent visual acuity on
mission, compared with 35 percent on
l examination. In 72 eyes of patients
treated with iodides routinely, the com-
ison was 26 to 29 percent. In compar-
the percentage of patients having poor
ual acuity on admission with the per-
tage on final examination, it was noted
t there was a 6-percent decrease in
ents treated routinely without iodides,
a 7-percent increase in patients
ted routinely with iodides.

he Cooperative Clinical Group's study
showed that iodides exert a harmful
uence in the treatment of active inter-
al keratitis but recognized them to be
of value in chronic cases. Although they
e been long recommended, the present
ty reveals *no justification for the con-
ed use of iodides, either orally or*

*intravenously, in active or inactive inter-
stitial keratitis.*

*Effect of treatment in relation to dura-
tion.*—Chart 9 shows visual acuity at final
examination of 200 patients with active
interstitial keratitis in relation to dura-
tion at onset of treatment. It is shown
that patients treated within 1 month
after the onset of interstitial keratitis
had much better visual acuity on final
examination than patients treated 2 to 3
months after onset and slightly better
visual acuity than patients treated 1 to 2
months after onset of the disease. This
applied to the visual acuity of the better
eye as well as the poorer eye.

*Effectiveness of treatment in prevent-
ing relapse.*—The term relapse refers to
a recurrence of inflammatory symptoms
of interstitial keratitis in a given eye
after previous inflammation has disap-
peared.

Table 4 includes only those relapses
occurring 1 year or more after onset in
296 patients with early active interstitial
keratitis on admission. In the table, the
cases have been divided by kind of treat-
ment and number of arsenical injections
administered in the first year after onset
of interstitial keratitis. *Routine treat-
ment supplemented with fever therapy
was superior to other forms of treatment
in preventing relapse.* Of 55 patients
given routine treatment plus fever ther-
apy only one had a relapse. It is to be
noted, however, that the fever therapy in
this instance consisted of only two injec-
tions of typhoid vaccine. Relapses after
other types of treatment were approxi-
mately the same, ranging from 13 to 18
percent.

The number of arsenical injections also
appeared to influence the percentage of
relapses. Of 198 patients treated with
less than 20 injections in the first year,
28 (14 percent) had a relapse of intersti-
tial keratitis compared with 8 percent of
98 patients treated with more than this
amount.

*Continuous versus intermittent treat-
ment.*—Chart 10 shows the effect of con-
tinuous, intermittent, or irregular treat-
ment on visual acuity of the better eye,

as well as of the poorer eye, of 376 patients at final examination. Visual acuity of untreated patients comprising the control group is also shown. Little difference is noted in visual acuity of the better eye of patients treated continuously, intermittently, or irregularly. As far as final visual acuity of the poorer eye was concerned, continuous treatment

was superior to intermittent or irregular treatment. Sixty-four percent of the patients continuously treated had good excellent visual acuity in both eyes compared with 47 and 48 percent of patients treated intermittently or irregularly. A smaller amount of poor visual acuity or blindness was observed in patients treated continuously or interm

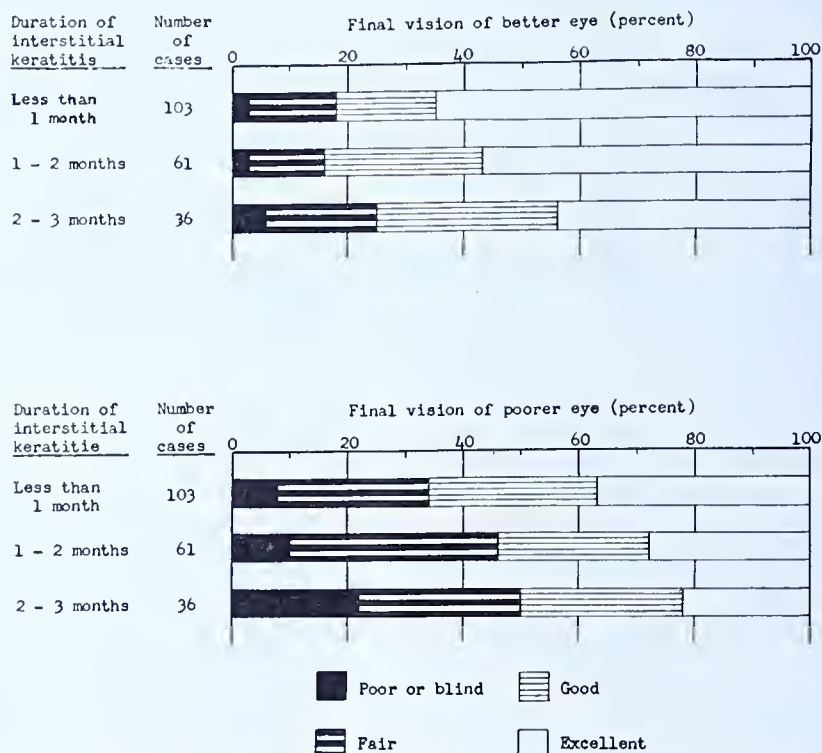


CHART 9.—Final visual acuity in relation to duration of interstitial keratitis at onset treatment.

TABLE 4.—Relapses occurring a year or more after onset of interstitial keratitis patients receiving various kinds and amounts of treatment in the first year

Kind of treatment administered in first year	Amount of arsenical treatment administered in first year							
	Less than 20 injections			20 or more injections			Total	
	Total cases	Cases relapsing		Total cases	Cases relapsing		Total cases	Cases relapsing
		Number	Percent		Number	Percent		
Routine only.....	72	11	15.3	27	2	7.4	99	13
Routine and iodides.....	76	11	14.5	28	4	14.3	104	15
Routine and fever.....	25	1	4.0	30	1	3.3	55	1
Routine, iodides, and fever.....	25	5	20.0	13	2	15.4	38	7
Total.....	198	28	14.1	98	8	8.2	296	36

1 Two injections of typhoid vaccine.

ently than in those treated irregularly. *Superiority of one arsenical compared with the other.*—It was not possible to determine the comparative effectiveness of the arsenicals employed since most patients were not treated exclusively with one arsenical. A comparison of old arsphenamine and nearsphenamine was

Table 5 is a comparison of visual acuity on final examination of 173 eyes of patients treated with the four principal types of fever employed. Although the number in each group is small, best results seemed to be obtained with malaria and hyperthermy, the two types producing the highest temperature. The percentage

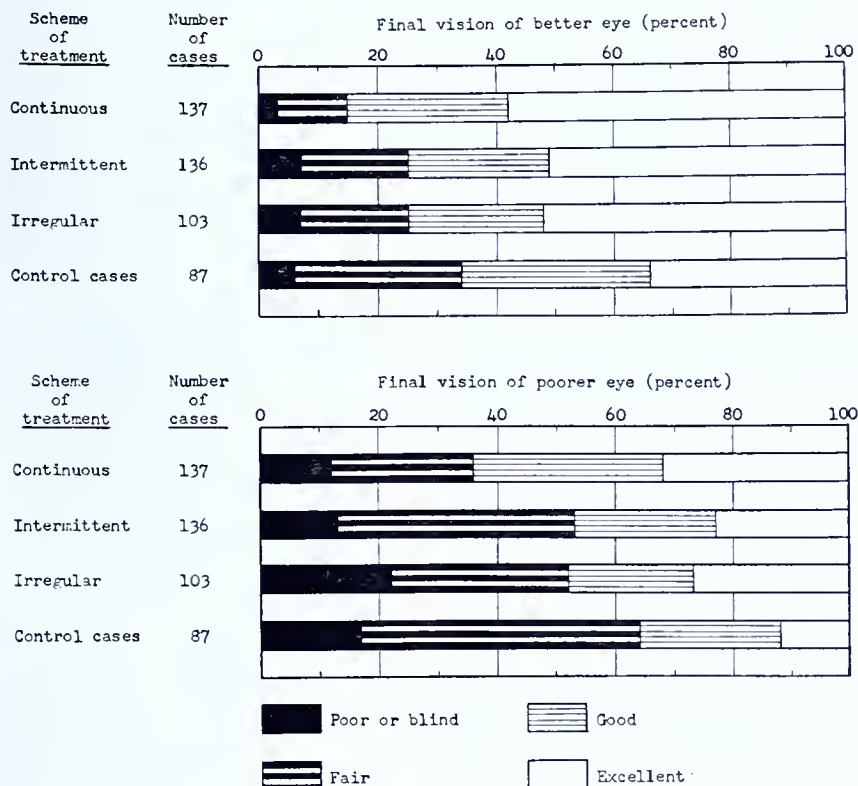


TABLE 10.—Final visual acuity of patients with interstitial keratitis following different plans of treatment compared with visual acuity of control group.

ssible. These drugs produced approximately the same percentage of excellent visual acuity.

Effect of fever therapy produced by different agents.—Fever therapy was employed in conjunction with routine treatment consisting of arsenicals and a heavy metal. The average number of fever treatments was eight. The average peak temperature produced by the following agents was: Malaria, 106.1° F.; typhoid vaccine and antigen H, 104.2° F.; pyrifera (colon bacillus), 105.8° F.; sterile milk (intramuscularly), 101.7° F.; artificial fever induced from 105.7° F. for vapothermy to 103.7° F. for hyperthermy.

of eyes with visual acuity of 20/20 and 20/60 or better on final examination after treatment with various fever producing agents was as follows:

	Visual acuity 20/20, percent	Visual acuity 20/60 or better, percent
Malaria -----	38	75
Hyperthermy-----	29	72
Sterile milk-----	32	53
Typhoid or antigen H-----	16	59

Recommendations for treatment of interstitial keratitis.—Obviously, it is better to prevent interstitial keratitis than to treat it. The objectives should be to

TABLE 5.—Effect of different types of fever therapy on final vision in 173 eyes patients with active interstitial keratitis

Final visual acuity	Typhoid or antigen 'H'			Malaria			Sterile milk			Hyperthermy (alone in combination)		
	Number	Percent		Number	Percent		Number	Percent		Number	Percent	
		Actual	Cumulative		Actual	Cumulative		Actual	Cumulative		Actual	Cumulative
6/6-----	18	15.5	15.5	9	37.5	37.5	6	31.6	31.6	4	28.6	28.6
6/9-----	21	18.1	33.6	4	16.7	54.2	2	10.5	42.1	4	28.6	57.2
6/12-----	10	8.6	42.2	2	8.3	62.5	1	5.3	47.4	-----	-----	57.2
6/15-----	20	17.2	59.4	3	12.5	75.0	1	5.3	52.7	2	14.3	72.0
6/21-----	16	13.8	73.2	-----	-----	75.0	2	10.5	63.2	1	7.1	79.1
6/30-----	8	6.9	80.1	2	8.3	83.3	4	21.1	84.3	2	14.3	93.4
6/60-----	12	10.3	90.4	1	4.2	87.5	1	5.3	89.6	1	7.1	100.5
—6/60-----	9	7.8	98.2	1	4.2	91.7	-----	-----	89.6	-----	-----	100.5
Blind-----	2	1.7	100.0	2	8.3	100.0	2	10.5	100.0	-----	-----	100.5
Total-----	116	100.0	-----	24	100.0	-----	19	100.0	-----	14	100.0	-----

treat the pregnant woman with syphilis to prevent congenital syphilis (5) and to treat early congenital syphilis to prevent interstitial keratitis (1). But it is also axiomatic that, once interstitial keratitis has set in, the sooner it is treated the greater is the chance for excellent vision.

The following scheme of treatment is recommended on the basis of the present study and the experience of the authors:

FEVER THERAPY

Malaria or hyperthermy should be employed as soon after onset as possible. If these types are not available, another fever-producing agent should be substituted. Because arsenicals and bismuth are antimalarial, they should be withheld during the course of induced malaria, but should be given in the intervals between fever bouts produced by other agents.

ANTISYPHILITIC TREATMENT

Neoarsphenamine or another trivalent arsenical (in full doses¹¹ in proportion to body weight) and bismuth subsali-

cylate should be given in alternating courses. Soluble bismuth, however, should be employed at the onset of treatment, simultaneous with arsenical therapy. The treatment should be continued according to the following schedule until approximately 30 injections of the arsenical and 60 of the bismuth have been administered.

Weeks

- 1 to 9 Neoarsphenamine, 10 weekly doses.
- Bismuth (soluble), 8 doses twice weekly, during first month.
- 10 to 19 Bismuth, 10 weekly doses.
- 20 to 29 Neoarsphenamine, 10 weekly doses.
- 30 to 39 Bismuth, 10 weekly doses.
- 40 to 44 Neoarsphenamine, 5 weekly doses.
- 45 to 54 Bismuth, 10 weekly doses.
- 55 to 59 Neoarsphenamine, 5 weekly doses.
- 60 to 69 Bismuth, 10 weekly doses.
- 70 to 73 Rest period.
- 74 to 83 Bismuth, 10 weekly doses.

It is imperative that treatment be continuous at least throughout the active stage of the disease.

The administration of iodides is not recommended.

Refraction after disappearance of inflammatory symptoms is always desired.

¹¹ Although initial use of large doses of an arsenical is generally to be avoided in treatment of other acute ocular lesions of syphilis because of the danger of Herxheimer reaction in the involved eye, pragmatically this does not apply to interstitial keratitis. It is apparent that this procedure in treating interstitial keratitis very rarely aggravates the disease in the eye or in other organs.

ble since improvement in visual acuity may result.

Summary and conclusions.—A report is made of an analysis of 532 patients with interstitial keratitis who were treated or served for at least 1 year.

Seventy-three percent of the patients are white, 27 percent were Negroes. Sixty percent were females. The median age at onset was 12 years for females, and 15 years for males.

Thirty percent of patients with inactive interstitial keratitis previously treated had a negative serologic reaction of the blood; 2.5 percent of patients with active interstitial keratitis who were untreated had a negative reaction.

In 532 patients other syphilitic manifestations were incident in varying degree, as follows: Hutchinsonian teeth, 1 percent; bone and joint involvement, 1 percent; labyrinthine disease, 10 percent; chorioretinitis, 8 percent; neurosyphilis (symptomatic and asymptomatic), 8 percent; paresis and taboparesis, 0.4 percent.

In 42 percent of patients both eyes were involved either simultaneously or within 1 month of each other. The percentage with second eye involvement increased slowly to the tenth year. At this time the second eye had become involved 79 percent.

The effect of different schemes of treatment on final visual acuity, with or without refraction, was graphically represented. Different schemes of treatment comprised routine (more than 20 injections of an arsenical or less than 20 injections in conjunction with a heavy metal), routine with iodides, routine with fever (malaria, mechanical fever therapy, vaccines intravenously), and routine with iodides and fever. Treatment was so classified as continuous, intermittent, and irregular.

It appeared that treatment administered in the inactive stage of interstitial keratitis was of limited value in improving visual acuity.

The importance of employing at least 20 injections of an arsenical in the active stage of the disease was emphasized.

Arsphenamine and nearsphenamine obtained approximately the same results.

The administration of iodides unfavorably influenced final visual acuity in both active and inactive interstitial keratitis.

The superiority of one plan of treatment over another involved an increase in the proportion of patients with excellent vision following treatment and not a decrease in the proportion whose sight remained poor.

Routine therapy supplemented with fever therapy was superior to other forms of treatment in preventing relapse. Of 55 patients thus treated only one had a relapse. Relapses after other types of treatment ranged from 13 to 18 percent. Relapse was more frequent in patients treated with less than 20 injections of an arsenical than in patients treated with more than 20 injections.

Continuous treatment was superior to intermittent or irregular treatment only insofar as concerned final visual acuity of the poorer eye, and in causing less poor visual acuity or blindness.

Best results were obtained in patients with active interstitial keratitis who were treated with an arsenical combined with the use of a heavy metal and fever therapy. This treatment resulted in the following final visual acuity (total eyes): Excellent (20/30 to 20/20), 51 percent; good (20/50 to 20/40), 17 percent; fair (20/200 to 20/70), 22 percent; poor (less than 20/200) and blind, 10 percent. This compared with the visual acuity (total eyes) of untreated patients (control group) as follows: Excellent, 24 percent; good, 27 percent; fair, 37 percent; poor and blind, 12 percent.

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DIAGNOSIS

Syphilis of the center of the face.

Harold N. Cole, James R. Driver and Hal E. Freeman. *Arch. Dermat. & Syph.*, Chicago, 43: 943-948, June 1941.

Syphilis of the center of the face has been known for many years but few instances have been reported.

The authors have observed the case of syphilis of the face here reported for many years. The patient, a man, is now 31 years old and has been blind for 20 years. He was the first-born child of a woman who subsequently had 7 miscarriages; he had a half-brother who lived. The mother, who was syphilitic, died in 1923 at the age of 46. She had chronic alcoholism and did everything possible to keep her child from seeing physicians. His history shows several admissions to the hospital: In May 1912 when he was about 4 years old he had a sore left eye, and roentgenograms of the right radius and ulna showed signs of syphilis. Mercury ointment was prescribed and used for about 2 months. At 4½ years, sores about the nostrils were noted and mercury ointment rubs were administered for about 8 months. He was next hospitalized for 9 months in 1917 for recurrence of sore nose, and by May 1918 the nose was entirely gone. At the age of 14 the entire center of the face had been eroded. The eyeballs could be palpated under-

neath the ulcerating tissue. In 1924 had many injections of various trivalent arsenicals and intramuscular injections of mercury and bismuth preparations. After this the patient remained a ward of the county and without treatment until January 1940, when he was admitted to the Cleveland City Hospital for further observation.

The entire center of the face, including the eyes, was replaced and overgrown by a pliable but firm scar. There was a single opening through which he ate, talked, and breathed. Hearing was good in the right ear and diminished in the left. He reads Braille and has adjusted himself well, considering his handicap. Serologic tests showed the Wassermann reaction to be strongly positive while the Kline diagnostic and exclusion tests gave negative results. The authors express the hope that this report will forcibly call attention of syphilologists and of roentgenologists to syphilis in the center of the face.

Tertiary syphilids of the nose. James S. Snow. *South. M. J.*, Birmingham 34: 713-717, July 1941.

The author presents a series of 42 cases of late syphilids of the nose seen at the University of Michigan Hospital during the past 15 years. These patients were from 26 to 76 years of age. The average age was 41. There were 31 women and 11 males in the group, a ratio of almost 3 to 1. There were 40 cases of acquired syphilis and 2 of congenital infection. Before coming to the hospital only 7 of the 42 patients knew that they had ever had syphilis. The duration of the nose lesion varied from 1 month to 12 years. The average duration was 13 months on admission. The duration of the syphilitic infection, as accurately as could be determined, varied from 9 months to 40 years. The average duration was 16 years. In 9 cases the syphilitic skin lesions were confined to the nose. In 26 cases (62 percent) there was a solitary lesion involving the nose and upper lip or adjacent cheek areas. In 32 cases (76 percent) the skin lesions were restricted to the face. In

the remaining 10 cases there were other syphilitic lesions elsewhere on the body surface. All of the tertiary lesions involving the skin of the nose were nodular and nodulo-ulcerative in character. In a few cases the nodules were superficial and there was a scale present, but in the large majority of cases the process was hypertrophic. This was especially true about the external nares, where the proliferative growth frequently occluded the openings. An actual tumorous mass was frequently produced in this area.

The chronic inflammatory process gave these lesions a dull erythematous color, which usually had a blue or violet hue. The areas involved were indurated and of a firm rubbery consistency. All were relatively painless. In some cases there was rapid destruction of nasal tissue. In addition to the damage to the skin and subcutaneous tissue which resulted in some permanent scarring in all cases, there was an actual destruction of the cartilages of the tip or alae of the nose in 13 cases (21 percent). This produced permanent disfigurement. The septum was damaged in 31 percent of the cases. There was simple perforation in 5 cases, and destruction of the septum and nasal bones, with resulting deformity of the bridge of the nose, in 8 cases.

In addition to the lesions of the nose and skin there were other manifestations of syphilis present in 65 percent of the cases. There was active involvement of the tongue, palate, or pharynx in 10 cases. The larynx was involved in 3 cases. One of these also had an extensive syphilitic tracheitis which necessitated bronchoscopy in order to remove large obstruction crusts. In 7 cases there was clinical evidence of cardiovascular syphilis, and in 4 there was syphilitic bone involvement other than that of the nose. Thirteen patients (31 percent) showed evidence of central nervous system involvement, as demonstrated either by abnormal spinal fluid findings or by definite neurologic signs. The serologic Kahn test was positive in all but one case, that of a 66-year-old woman who had acquired her infection 40 years pre-

viously. Her nose lesion had been present for about 10 years and showed little evidence of activity at the time of examination.

Tertiary syphilitic lesions of the nose must be differentiated from the following conditions: (1) Tuberculosis cutis, including lupus vulgaris and tuberculosis cutis orificialis; (2) epithelioma; (3) acne rosacea and rhinophyma; (4) rosacea-like tuberculid, lupus erythematosus, sarcoid; (5) infectious eczematoid dermatitis; (6) impetigo with marked crusting; (7) ringworm; (8) bromoderma and iododerma; (9) blastomycosis; (10) actinomycosis; (11) leprosy; (12) rhinoscleroma; (13) glanders. Several of these patients had a syphilitic laryngitis which had previously been considered tuberculous. The differential diagnosis of these cases is discussed in detail.

The final cosmetic results obtained in these cases was surprisingly good. The lesions rapidly involuted with therapy consisting of courses of arsphenamine, neoarsphenamine, or mapharsen, together with bismuth and potassium iodide. However, in those cases in which destruction of the cartilages or small bones of the nose had occurred, the resulting defect was permanent. Treatment of those patients with cardiovascular, hepatic, or central nervous system syphilis, or with syphilis of the larynx, was given cautiously to avoid serious treatment reactions which might prove fatal.

Local trauma and inflammation, especially that accompanying upper respiratory infections (chronic sinus infections, colds in the head, etc.) seemed to be an important factor in the localization of the syphilitic process in a significant number of the cases studied.

Are radial lip scars a dependable sign of congenital syphilis? W. Krantz. *Dermat. Wehnschr.*, Leipzig, 112: 369-374, May 10, 1941.

After reviewing the literature on lip scars, the author points out that although congenital syphilis is not the only cause of these scars, it is undoubtedly the principal cause. They are of great diagnos-

tic importance when they are well marked and form small indentations into the red portion of the lip, when they extend in the form of whitish furrows far into the surrounding skin of the face. The blood should be tested, however, and other signs of congenital syphilis sought so that, whenever possible, the diagnosis will not be based on lip scars alone. The less characteristic the scars are the more they lose in diagnostic value.

Roentgenographic diagnosis of congenital syphilis in unerupted permanent teeth. Bernard G. Sarnat, Isaac Schour and Robert Heupel. J. A. M. A., Chicago, 116: 2745-2747, June 21, 1941.

As demonstrating the value of routine intraoral roentgenograms of unerupted permanent teeth as an aid in the early diagnosis of congenital syphilis the authors discuss the case of a Negro girl. A diagnosis of congenital syphilis was made when she was 2 years of age. Roentgenograms of the long bones were of no diagnostic aid. Treatment consisted of acetarsone alternated with bismuth salicylate.

A roentgenographic diagnosis of congenital syphilis was made on the unerupted permanent central incisors and first molars of the child when she was 4 years of age, and this was confirmed clinically 2 years later when the teeth had appeared in the oral cavity. The teeth showed disturbances in the developmental phases which occur during the neonatal period and earliest infancy. The effects were different in the growing deciduous and permanent teeth, depending on the developmental stage active at the time. The deciduous teeth, active in the formation of enamel, showing hypoplasia; the permanent teeth, active in morpho-differentiation, showed a disturbed dentino-enamel junction with a resulting characteristic distortion of the crown. The child had had bronchopneumonia during infancy and possibly rickets; the presence of hypoplasia of the enamel in the permanent teeth was probably a record of this systemic disturbance,

which had been present from about the third to the tenth month.

The changes in the teeth are permanent while those in bone are subject to resolution. Had intraoral roentgenograms been taken when those of the long bones were (when she was 2 years old), the diagnosis of congenital syphilis would probably have been confirmed by the dental abnormalities.

The authors believe that roentgenograms of the unerupted permanent teeth as well as of the long bones should be used as an aid in the early diagnosis of congenital syphilis.

Genitoinfectious lesions in the male complicated by gonorrhea. George Shropshire and Donald K. Hibbs. Am. J. Syph., Gonorr. & Ven. Dis., St. Louis, 25: 435-444, July 1941.

Since gonorrhea is perhaps the most prevalent venereal infection, estimated to be three to five times as prevalent as syphilis, it is not uncommon to find the disease associated with other genitoinfectious lesions in the male. The authors state that the physician's first responsibility is to establish the presence or absence of syphilis in cases of gonorrhea bearing in mind the relative frequency of intrameatal primary lesions.

During 1939, 306 cases of primary and secondary syphilis in male patients were diagnosed at the Municipal Social Hygiene Clinic of the Chicago Board of Health. In 33 (10.7 percent) of these cases, primary or secondary syphilis was observed in patients with gonorrhea. Of 161 cases of primary syphilis, gonorrhea was found in 23 instances (14.2 percent). In 145 patients with secondary syphilis gonorrhea was observed in 10 cases (6.8 percent). Kemp and Shaw observed that in 500 cases of gonorrheal urethritis in the male, there were 10 cases (2 percent) with infectious syphilis.

Coincidental venereal disease lesions, e. g., syphilis, chancroid, granuloma inguinale, venereal lymphogranuloma, in various combinations may be associated with gonorrhea in the same patient. A review of 73 cases of chancroid in the male

revealed that in 3 patients (4.1 percent) chancroid and gonorrhea were found to be associated conditions. In 105 cases of venereal lymphogranuloma in men, there were 4 (3.8 percent) in which mixed infection with gonorrhea occurred. In 3 out of 7 cases of granuloma inguinale in the male, observed during the past year, gonorrhea was a complication. Genital ulcers, syphilis, and gonorrhea, giving rise to erosive balanoposthitis, is sometimes associated with gonorrhea. These lesions are of great importance because the primary lesion of syphilis may arise as a simple balanoposthitis.

Gonorrhea may also be associated with lesions such as verruca acuminata, scabies, herpes progenitalis, lichen planus, infected sebaceous cysts, and simple infected abrasions. Although the diagnosis is frequently obvious, these lesions must be subjected to repeated dark-field examinations, since syphilis may occasionally be superimposed. The possibility of malignancy involving the external genitalia in the male must be emphasized.

In the authors' experience the concurrent administration of neocarsphenamine intravenously to patients with syphilis who were receiving small doses of sulfanilamide orally for the treatment of gonorrhea, produced no untoward reaction. This observation also held true for the intramuscular injection of fuadin in cases of mixed infection with granuloma inguinale and gonorrhea.

According to the authors, the effectiveness of sulfanilamide in chancroid and venereal lymphogranuloma has greatly simplified the treatment of these diseases, whether associated or not with gonorrhea.

lymphogranuloma venereum. Report of an unusual example involving the lymphatic glands of the buttock and adjacent regions. Maurice J. Costello and Gerard DeOreo. Arch. Dermat. & Syph., Chicago, 43: 997-999, June 1941.

A Negro seaman, aged 35 years, was admitted to Bellevue Hospital, giving a history of having had gonorrhea. In 1937 he had a right inguinal bubo which

had discharged pus from several openings. In May 1938 a smaller swelling developed on the right buttock, and several months later a hard swelling occurred on the right hip which later discharged pus. Examination showed in the right inguinal suprapubic and genitocrural regions and on the right buttock and right hip a massive, tense, shiny, hyperpigmented induration with multiple fistulous openings. The Wassermann reaction of the blood was repeatedly negative, but the Kahn reaction was positive. The intracutaneous and intravenous injections of Frei antigen of the mouse-brain and chick-embryo types gave positive reactions. Chancroid, scrofuloderma, actinomycosis, blastomycosis were ruled out, as was also tuberculosis. To confirm the diagnosis of venereal lymphogranuloma there were typical inguinal lymphadenopathy, a positive reaction to the intradermal injection of Frei antigen, and a histologic picture which showed many of the changes usually seen in this disease.

Gonococcal infections. Diagnosis and criterion of cure. Adolph Jacoby. J. Michigan M. Soc., Lansing, 40: 435-439, June 1941.

The diagnosis of gonorrhea in women is very frequently overlooked both in private practice and in institutions. This is shown by the fact that of the 12,807 cases of gonorrhea reported in 1939 in New York City 2,827 were female, and of 71,090 cases reported in England and Wales for 1935 and 1936, 15,447 were female. The reason for the marked difference in reporting cases in the male and female lies largely in the belief of most physicians that the diagnosis can be made only on laboratory evidence.

The diagnosis of gonorrhea must be made from a summation of the various factors obtained from the history, symptomatology, physical signs, and laboratory reports. The usual laboratory evidence employed is the smear, culture, and complement fixation test. In an analysis of 1,482 women in prison who were found to have gonorrhea, it is shown that 65.8

percent of the cases would have been overlooked if the smear alone had been used as a criterion, and if the diagnosis had been made from the culture alone 47.2 percent would have been missed. The complement fixation test at present is of very uncertain value. In an examination of 4,262 prostitutes only 22.4 percent were discovered to have gonorrhea as a result of smear and culture examination.

In no other diagnosis is a detailed and thorough history so essential as in the diagnosis of gonorrhea in women. This history must include a searching inquiry into the past existence of urinary symptoms and vaginal discharge.

In view of the wide use of the sulfonamide compounds in treating gonorrhea, it is especially important that the criteria of cure be sufficiently searching to uncover any incompletely cured infection. The only sure method of determining cure is by prolonged observation and persistently negative physical symptoms, physical signs, and smears and cultures. Provocative measures in the female have been abandoned, and the author thinks that in the male they are not of much value.

The Frei test for lymphogranuloma venereum. Experiences with a new antigen (lygranum) prepared from infected yolk sac of developing chick embryo. S. Edward Sulkin. J. A. M. A., Chicago, 116: 2663-2665, June 14, 1941.

The author says that antigen prepared from the yolk sac of the developing chick embryo infected with the virus of venereal lymphogranuloma can replace that prepared from infected mouse brain or from human pus for performing the Frei cutaneous test. On the basis of an analysis of the results obtained in 42 patients with venereal lymphogranuloma and 20 non-lymphogranulomatous persons, this antigen (lygranum) was found to be superior to mouse-brain antigen in sensitivity and specificity. In 11.9 percent of the cases of venereal lymphogranuloma the papules appearing in reaction to control mouse-brain material were 5 mm. or more in di-

ameter and were indistinguishable from those seen in positive Frei reactions. In each of these cases a positive diagnosis could be made with the yolk sac antigen or with the material from human pus. Throughout the investigation the reactions to mouse brain were invariably more intense than those resulting from human pus or yolk sac material. No specific papules were produced in 29 of the 42 lymphogranulomatous persons receiving control mouse-brain material while only 16 patients showed reaction to the lygranum-control material. The results substantiate recently reported observations by Grace, Rake and Shaffer.

TREATMENT

Preliminary report of sulfanilamide, sulfapyridine, and local therapy in gonococcal infection in women. J. Close Hesseltine, Lucile R. Hac, Frederick L. Adair and Donald K. Hibbs. Am. J. Syph., Gonorr. & Ven. Dis., St. Louis 25: 454-460, July, 1941.

The authors present a preliminary report of a study which has been started to evaluate current therapies used in gonococcal infection in women. The intention was to follow a sufficient number of carefully controlled cases, checked over a long period of time by smear and culture in order that definite conclusions might be drawn concerning the type and length of treatment and the requirements which should be fulfilled before a patient might be discharged as cured. The plan of procedure and some of the results obtained are presented. The series thus far completed is too small to be used as a basis for final conclusions.

Since many authorities believe that gonococcal infection in women runs a self-limited course, it would have been ideal to have had a series of untreated patients for controls. That proved to be impossible. Instead, local treatment was used for comparison with the results from

hemotherapy. Local treatment consisted of the application of 2 percent merurochrome to the cervix and cervical anal and the instillation of 5 percent silver proteinate into the urethra. The patients in whom local treatment failed were given drug therapy when possible.

The dosage of sulfanilamide consisted of 4.0 gm. (60 grains) in 4 doses daily for 5 days followed by 2.6 gm. (40 grains) daily for 10 days. The dosage of sulfapyridine was 3.0 gm. (45 grains) daily for 5 days, followed by 2.0 gm. (30 grains) daily for 4 days. Those patients who did not respond favorably to treatment were given a second course of the same drug a week later, and, if they still did not respond, they were given a week of rest and then treated with the other drug. Some of the patients who did not respond to either the sulfanilamide or the sulfapyridine were treated with sulfathiazole.

All of the patients were ambulatory; 10 percent were Negroes. Diagnosis in every case was based on cultures of the gonococcus. Criteria of cure were rigid. The patients were followed up through three menstrual cycles with smears and cultures taken before, during, and just following menstruation. In order to determine how soon the patients became negative and if and when a relapse occurred, smears and cultures were made two or three times a week during treatment. After the first negative culture was obtained, smears and cultures were made twice a week for the first month, once a week during the second month, and once in 2 weeks during the third month—a minimum of 17 smears and cultures for each patient.

Of 41 patients given local treatment, 8 (20 percent) were cured, and 33 (80 percent) were not cured. Seventeen of the failures were given chemotherapy, to which 16 responded favorably. The 1 failure gave evidence of reinfection.

Of the 46 patients given sulfanilamide, 22 (70 percent) were cured, and 14 (30 percent) were not cured. Of the 14 not cured, 6 showed signs of reinfection; 8 did not show such evidence. The prob-

able drug failure was 17 percent for this series.

Of the 63 patients given sulfapyridine, 45 (71 percent) were cured, and 18 (29 percent) were not cured. Of the 18 not cured, 14 showed evidence of reinfection, and 4 showed no such evidence. The probable drug failure was 6 percent for this series.

Thus, with sulfapyridine therapy, the duration of treatment was shorter, the dosage was smaller, the response was quicker, the percentage of failures was lower, and the patients complained less of toxic symptoms than with sulfanilamide.

The present status of the gonorrheal vaginitis problem. Robert M. Lewis, *Am. J. Syph., Gonorr. & Ven. Dis., St. Louis*, 25: 496-503, July 1941.

The author states that in general the fundamental principles of management of gonococcal infections of men, women, and children are the same, although each has problems which differ in detail. Keyes' aphorism that our grandfathers' generation had gonococcal infections and recovered with no adequate treatment is a memorable one. In the past forgetting the tendency to spontaneous cure has led to at least two unfortunate results: (1) The curative results of different preparations and procedures have been miscalculated, as it is now realized that spontaneous recovery accounted for most of the reported cures. This is especially true of vaginitis cases. (2) The physician, feeling a great responsibility to cure his patient rather than to let the patient recover, often made the infection worse by the vigor of his local treatments.

It is not possible to estimate the incidence of gonococcal infections of girls from health department reports. A great majority of such cases are not reported. In 1939 only 316 cases of the disease in little girls were reported by the Department of Health of New York City. Most cases of vaginitis in children are not of gonococcal origin. With the development of practical methods of culture, it is now possible to eliminate many cases

erroneously diagnosed as gonococcal infection by spreads alone.

A considerable proportion of children's gonococcal infections occur during the first 18 to 24 months of life. Their source has never been definitely determined. McLeod, in an unpublished study, reports that of a group of 47 girls born of mothers with gonococcal infections at the time of delivery, 38 yielded positive spreads at some time during the first 18 months of life. Of these 38, only 15 showed clinical evidence of infection before the age of 1 month, and 18 first showed clinical evidence of infection in the period between 5 and 18 months after birth. Culture studies were not available and the diagnosis depended on positive spreads and clinical symptoms.

Miss E. P. Rice, Director of Medical Social Service of the New Haven Hospital, found that, in 8 of 15 cases of little girls with gonococcal vaginitis (the ages of the patients ranged from 5 to 12 years), histories of sexual contact with men or boys was disclosed by painstaking inquiry.

Children in New Haven are returned to school while still infected and under treatment, but not if the vaginal discharge is profuse. This policy has been successful, appears reasonable, and is in force elsewhere. It increases the responsibility of schools in supervising the children's hours of recreation.

Criteria of cure should include negative cultures from the dimple of the small external cervical os, which contains vaginal contaminants. For practical purposes a child may be discharged as presumably cured after 3 months during which she has been clinically well with persistent negative spreads and cultures taken from the vagina. Presumably, even some such patients may have a later recurrence. Without a formal announcement of "cure" such children may attend school and return to intimate association with other children, although they should be kept under careful observation for at least a year or longer.

The author states that in the treatment of many types of nonspecific vaginal infections and occasionally secondary vagi-

nit, which may succeed gonococcal infections, the estrogens are still of great value. Results with sulfanilamide in cases of gonococcal vaginitis in children have not been very satisfactory. Schauler, in a summary of a large number of reports by different authors, found that an average figure for successful treatment with sulfanilamide probably is between 30 and 50 percent. Sulfapyridine seems to be the most effective drug in this condition (at the time the author made this report). Sulfathiazole should prove to be an improvement over sulfapyridine.

The management of gonorrhea for national defense. Oscar F. Cox. *Bull. Genitoinfect. Dis.*, Boston, 5: 1-5, May 1941.

Not the least important of the many factors upon which the efficiency of an army depends is the skill with which the medical profession manages the gonococcal infections. The incidence of infection among civilians following demobilization possibly may not be kept from rising, but the loss of time resulting from the infection can be greatly reduced.

The most efficient methods for managing gonococcal infections are not yet in general use. In some places local treatment is still relied upon to the exclusion of modern chemotherapy. In spite of the fact that sulfapyridine and sulfathiazole are known to be 3 to 4 times more efficient than sulfanilamide, during the past 6 months 7 times more sulfanilamide than sulfapyridine and sulfathiazole combined was sold to the American public.

Cox believes it to be a sound public health procedure to prescribe a few sulfathiazole tablets for the male or female patient while waiting for the laboratory reports from smears or cultures. By this means the extension of the infection will have been prevented, and no harm will have been done to the patient in those rare instances in which the purulent discharge was not due to the gonococcus.

In some military establishments it is the practice to confine all patients with gonococcal infection to the hospital for a minimum of 6 weeks. Cox believes that

this is unjustifiable on any grounds. Modern treatment will render 80 percent of all early gonococcal infections symptom-free in less than 2 weeks. Confining soldiers to camp until they have been cured will afford ample protection. Chemotherapy plus adequate drainage will produce a high cure rate in chronic gonorrhea; patience and gentle treatment will ultimately be rewarded with success.

It is the patriotic duty of physicians, both in and out of the armed services to familiarize themselves with the modern methods for treating these diseases so that the expected rise in incidence can be controlled more efficiently than it was in 1917 and 1918.

Sulfonamide therapy in male gonorrhea. A comparative study. Rogers Deakin, Morris Wortman and Richard La-Force. *Am. J. Pub. Health*, New York, 31: 682-686, July 1941.

This report covers the treatment with seven different chemotherapeutic agents of 519 men with gonorrhea. Local therapy also was used with sulfanilamide, benzene-sulfone-dimethylamide, sodium benzene-sulfone-dimethylamide, and sulfanilamide-magnesium oxide. No local therapy was used with sulfapyridine, sulfamethylthiazole, or sulfathiazole. The average daily dosage of the drugs was 2.0 gm. of sulfapyridine, 4.0 gm. of sulfamethylthiazole, 4.0 gm. of sulfathiazole, and 2.7 gm. of each of the other four drugs. The average total dosage ranged from 20 gm. of sulfamethylthiazole and 20 gm. of sulfathiazole to 75 gm. of sulfanilamide. Criteria of cure included three negative cultures made 1, 5, and 9 weeks after treatment was discontinued.

The number of patients treated with each drug, and the percentage of smears and cultures negative by the tenth week were as follows: (1) Sulfanilamide, 95 cases, 77 percent; (2) benzene-sulfone-dimethylamide, 61 cases, 78 percent; (3) sodium benzene-sulfone-dimethylamide, 191 cases, 83 percent; (4) sulfanilamide-magnesium oxide, 50 patients, 74

percent; (5) sulfapyridine, 47 patients, 97 percent; (6) sulfamethylthiazole, 37 patients, 93 percent; and (7) sulfathiazole, 38 patients, 100 percent. The authors are studying the results of treatment with sulfathiazole in 167 additional men.

Coordination of an adequate laboratory service and an efficient case-finding and case-holding service with close medical supervision was made possible by assistance with Federal funds provided through the Missouri State Board of Health. This permitted accurate clinical and bacteriologic comparison of different drugs under carefully controlled conditions. The authors conclude that sulfathiazole seems to be the most effective of the drugs at present available commercially for the treatment of gonorrhea in men. The rapidity with which it renders a male patient noninfectious, together with the fact that it is well-tolerated and relatively nontoxic, permits its use on a wide scale for gonorrhea.

Toxic effects of sulfathiazole used in treatment of chancroidal infection.

Earl A. Glicklich and David S. Sherman. *Arch. Dermat. & Syph.*, Chicago, 43: 992-996, June 1941.

A 55-year-old white man was admitted to the Boston City Hospital in November 1940 with a complaint of penile ulceration and discharge. His history revealed several attacks of urethral discharge and, 14 years previously, a penile lesion followed by a swelling of the inguinal nodes in the left groin. After examination, the diagnosis was chancroidal infection, with chronic gonorrheal urethritis and healed venereal lymphogranuloma.

He was given 6 gm. of sulfathiazole daily by mouth. On the 4th day his temperature rose, and the next day there developed malaise, marked prostration, nausea, headache, burning and itching of the eyes, and a maculopapular eruption above the knees and elbows. Through error the drug was continued 2 days longer, by which time the scleras and conjunctivas became injected, and the joints became tender and swollen. Cul-

ture of the fluid aspirated from the left knee showed that it was sterile; the sulfathiazole concentration showed a total of 4.1 mg. per 100 cc. During the sulfathiazole therapy the patient's discharge had ceased, the chancroidal ulcer was almost healed, and the nodes were subsiding. One week later he was again given 1 gm. of sulfathiazole every 6 hours. After the fourth dose the same reactions he had had before returned. The drug was discontinued, and in 12 hours the patient was practically symptomless.

The tenderness, swelling, and effusion of the joints represented toxic manifestations rather than a gonococcic arthritis since the symptoms recurred on the readministration of the drug, the synovial fluid was clear, serous, and sterile, and the synovial fluid contained sulfathiazole.

Rapid treatment of early syphilis with multiple injections of mapharsen. Preliminary report of 275 cases treated with mapharsen alone and 141 cases treated with mapharsen and fever. Evan W. Thomas and Gertrude Wexler. *Am. J. Pub. Health*, New York, 31: 545-556, June 1941.

The authors report the results of the treatment of 275 patients with early syphilis at Bellevue Hospital in New York who were given multiple injections of mapharsen over a period of 6 to 10 days and 141 such patients who were given the rapid treatment with multiple injections of mapharsen plus fever therapy. There were no facilities for the continuous drip method at Bellevue Hospital.

The intensive treatment was begun in December 1939 by giving 2 injections of 0.06 gm. mapharsen daily for 10 days. After treating 38 patients in this manner, the period of treatment was shortened from 10 to 6 days because of the occurrence of a number of early acute arsenical erythemas which caused the discontinuance of treatment on the seventh or eighth day. The patients had tolerated the treatment so well that it was decided to increase every dose from 0.06 gm. to 0.1 gm. and to give the drug twice a day

for 6 days. As women had tolerated the 10-day treatment with a total dosage of 1.2 gm. as well as men, no distinction was made in dosage between the sexes in the 6-day treatment.

Except for some nausea and vomiting this treatment was tolerated remarkably well until the 111th case, a 23-year-old Italian woman who died from hemorrhagic encephalitis. It was then decided to continue giving the treatment to selected patients, but to reduce the dosage and to increase the amount of laboratory study of each patient. In males, each dose of mapharsen was reduced to 0.0 gm. or 0.09 gm. instead of 0.1 gm.; and in females, to 0.06 gm. or 0.07 gm. The total dosage, therefore, varied from 0.7 gm. to 1.08 gm. in 6 days. In addition to the usual blood counts, blood chemistry, and liver function tests, careful spinal fluid examinations were made on each patient before and immediately after treatment.

Another case of hemorrhagic encephalitis occurred in a 26-year-old Italian man following the 11th injection of 0.06 gm. of mapharsen in 5½ days. This patient was desperately ill for 48 hours, but he recovered.

A third case of hemorrhagic encephalitis developed in a 21-year-old Polish man following the 11th injection of 0.07 gm. of mapharsen in 5½ days. He recovered.

It was decided to reduce the total dosage of mapharsen and to combine it with fever therapy. The plan of treatment was to give 2 injections of 0.06 gm. mapharsen on the first day, 1 injection of 0.06 gm. mapharsen on each day thereafter for 7 days, and to induce fever by typhoid vaccines intravenously on the 2d, 4th, 6th, and 8th days. The association of typhoid vaccines intravenously and mapharsen on the same day caused much distress to many patients—headaches, nausea, and vomiting forming the chief complaints. The number of vaccine injections was reduced to 2, and they were not given on the same days with the mapharsen. In addition, the total dosage of mapharsen was increased from 0.54 gm. to 0.84 gm., or more in selected cases.

Although only a few patients have been treated in this way, there seems to be less discomfort than with the previous method. Mapharsen alone is still used in pregnant women or patients with active pulmonary tuberculosis.

Because the combined treatment with fever and mapharsen was started less than 6 months ago, the results of treatment are reported only on those who were given mapharsen alone. Of 142 patients treated with 1.08 gm. to 1.2 gm. of the drug, 86.3 percent had probable favorable results, 3.2 percent were still seropositive, and 10.5 percent relapsed or were reinfected. Of 59 cases treated with 0.66 to 0.84 gm. of mapharsen, 76.9 percent had probable favorable results, 7.7 percent were still seropositive, and 15.4 percent relapsed or were reinfected.

Note on metrazol in general paresis.

A psychosomatic study. Vivian Bishop Kenyon, David Rapaport and Milton Lozoff. *Psychiatry*, Baltimore, 4: 165-176, May 1941.

Despite the indubitable results of modern methods of treatment of general paresis by hyperpyrexia and tryparsamide, in many cases, often even in serologically significantly improved ones, no remission of the psychosis follows. Kenyon suggested the application of metrazol in a case of this type; the psychosis responded to the metrazol treatment, and the patient was returned home shortly afterwards, much improved. The authors discuss the theoretical situation in regard to the psychosis of general paresis in order that light may be shed on the theoretical significance of this result. The organic damage is so impressive in general paresis and the dementia so outstanding that the possibilities for psychologic studies have seemed discouraging.

A survey of the literature of the psychosis of general paresis shows that even early observers felt that the previous personality development played an important role in the make-up of this organic psychosis; that psychoanalytic literature found the content of delusions can be understood by means of psycho-

analytic knowledge; that there is difference of opinion on the question whether the dementia or the regression is the essence of this psychosis; and that the conditions of reversibility of the psychosis are unclarified and so is the extent to which dementia is psychogenic.

The discussion of malarial treatment indicated that the psychosis, since it yields to nonspecific treatment, follows the laws of psychodynamics. It was also concluded that while the deterioration might be correlated with the organic damage, the persistence or nonpersistence of the psychosis seems to depend on a more general factor, probably on the previous personality development. The effect of treatment by sodium amytal indicated that a paretic psychotic reacted to this drug in a fashion similar to functional psychotics.

The experimental use of metrazol in a group of 16 patients is reported with favorable results appearing in 3 of the 12 patients who had previously not responded to specific therapy, and in 2 of the 4 patients who had received no specific treatment prior to the metrazol. Some degree of improvement was noted in 5 others of the group. These results appear to confirm the inference from the effect of sodium amytal that in at least some cases of paresis the psychosis can be reversed to varying degrees by the same measures used in the treatment of the functional psychoses, thus indicating the importance of psychogenic factors in the production of the paretic psychosis.

It is seen by the Rorschach test on hyperpyrexia and metrazol-treated paretics that the paretic patient retains, after improvement, the bodily preoccupation and inclination to depression which have been described as initial phenomena of the onset of this psychosis. Thus, the way to regression seems to remain open after improvement. The tests indicate in a majority of the cases an intimate relation of paretic psychoses to circular psychoses. The Babcock deterioration tests indicated that great deterioration persists even in the best improved cases. The Szondi test appeared to indicate that

there might be some predisposing personality pattern in the person developing parietic psychosis. The method of using drugs and psychologic tests as variations of the experimental situation is suggested as a method of psychosomatic research.

Arsphenamine dermatitis provoked by exposure to the sun with regression followed by completely black pigmentation of the entire body. Meeting of Northwest German Dermatologists, Hamburg, November 1940. Dermat. Wehnschr., Leipzig, 112: 271, Apr. 5, 1941.

The case of a 20-year-old man is reported. He contracted syphilis in March 1940. When he had received half of his second course of antisyphilitic treatment he exposed himself to the sun. This was followed by the appearance of a generalized dermatitis resembling in every way an actinic dermatitis. Treatment was discontinued. The dermatitis cleared up but was followed by marked generalized, macular pigmentation and complete loss of hair. This pigmentation persisted. The Wassermann reaction was negative at the time of this report.

Treatment-resistant syphilis with recurrence at the site of the primary lesion. Meeting of Northwest German Dermatologists, Hamburg, November 1940. Dermat. Wehnschr., Leipzig, 112: 279, Apr. 5, 1941.

Early in September 1939 a 33-year-old woman noticed on her chin a lesion which she considered to be a mosquito bite. She saw a physician who called it a furuncle and who incised it. Two weeks later there was marked enlargement of the submaxillary lymph nodes. Four weeks later a biopsy was taken in a surgical clinic and the patient referred to the writer. The cut surface of the lesion exuded abundant serum containing *Spirochaeta pallida* as demonstrated in the dark field. At this time she also had a generalized skin eruption. She received 2 courses of combined antisyphilitic treatment under the influence of which

the chancre gradually healed. During the third course papules appeared on the right elbow, left eyebrow, and left buttock together with a breakdown of the primary lesion. She was given malarial therapy which was followed by disappearance of the papules but the chancre on the chin was still markedly infiltrated. The Wassermann reaction was strongly positive. Histologic examination showed dense perivascular infiltration of plasma cells. Diagnosis: late secondary-early tertiary syphilid.

Further experiences with mapharsen in syphilis. Report of a fatality. George W. Creswell and George B. Roth. J. Ann. District of Columbia, Washington, 10: 230-233, June 1941.

Further clinical experience with mapharsen in 306 cases of syphilis confirms the writers' previous prediction that this drug would become one of the approved agents in antisyphilitic therapy. All of the 306 cases now reported were out-patients, 251 being in a public health clinic, 34 in a university hospital clinic and 21 private office cases. All of the cases had reacted unfavorably to one of the arsphenamines, the type of reaction being nausea and vomiting in 4 percent; nitritoid reaction, 27 percent; itching and rash, 12 percent; jaundice, 6.4 percent; other reactions 12.6 percent. Seventy-two percent of the series showed no significant reaction to mapharsen, 1 percent reacted to mapharsen less severely, and 14 percent as severely or more severely than to the arsphenamines. In this series the complaint of pain in the arm and shoulder, which was common in the former series, was lacking. The authors feel that this might be due to the use of a larger needle (20 gauge) which allowed the drug to be given more rapidly.

Included in the group of cases with severe reactions was one of early latent syphilis in which death from aplastic anemia occurred 17 days after the fifth injection of a second series of mapharsen given concurrently with bismuth. The total dose of mapharsen was 0.62 gram

The authors are inclined to believe that bismuth may have played a part in the production of the blood complication, since it is well established that bismuth used concurrently with mapharsen not only produces a more rapid healing of the early cutaneous lesions but also affects and maintains an early complete reversal of the serologic reactions more frequently than without bismuth. Kirkham and Perlmutter have reported a case of aplastic anemia in which bismuth and mapharsen had been used concurrently.

PATHOLOGY

Syphilitic thoracic aneurysm in young adults. Byron Evans. *Brit. M. J.*, London, 1: 851-854, June 7, 1941.

According to the author, syphilitic thoracic aneurysm rarely occurs in patients under the age of 30. Only 2 of the 840 patients with such aneurysm admitted to the London Hospital during the past 46 years were below this age. These two, with a third who was recently under the author's care, are described by the author. In the first two cases, a history of primary infection was obtained. In the third case no stigmas of congenital syphilis were found, and the Wassermann reactions in both the mother and sister of the patient were negative. The author reviews the literature on aortitis in congenital syphilis, onset of aortitis in acquired syphilis, and the age incidence of aneurysm. Congenital syphilitic mesaortitis does occur, but the incidence of aneurysmal dilatation is very rare. Symptoms of thoracic aneurysm may appear within 10 years of the primary syphilitic infection, but in the majority of cases the period is 15 to 20 years. The maximum incidence of aneurysm of the thoracic aorta is in the sixth decade.

CASE 1. A 29-year-old man (seen in 1899) began to have a cough, increasing hoarseness, pain in both arms, and diffi-

culty in breathing about 7 years after contracting a penile chancre, and about 3 months before death. He had been treated with potassium iodide for the chancre 7 years before for 7 months. On admission to the hospital he was orthopneic, hoarse, both vocal cords were paralyzed, and he had a persistent croupy cough. There were "tissue paper" scars on both legs. The right pupil was smaller than the left. There were clinical signs of tracheal obstruction due to diffuse aneurysm of the aortic arch. The day after admission to the hospital tracheotomy was performed without relief, and the patient died after 4 days. The necropsy confirmed the clinical diagnosis. The macroscopic description of the aorta at the necropsy suggested that the aneurysm was due to aortitis rather than to mucous degeneration of the media, or to severe medial degeneration associated with atheroma.

CASE 2. The patient was a 28-year-old man who began to have shortness of breath on exertion, periodic attacks of severe coughing without expectoration, and dull aching pain behind the sternum and in the left axilla that sometimes radiated down the inner side of the left arm. (This was in 1913, 8 years after he had contracted syphilis and had been treated for 3 months with injections.) He died 2 months after these symptoms developed. About a month before death he began to be very breathless and could sleep only with his head on a table placed in front of him. His Wassermann reaction was positive. About 10 days before death he was pale and orthopneic, and he coughed constantly. There were signs of emphysema, and crepitations were heard over both lung bases. There was edema of both legs. Fluoroscopic examination showed a large pulsating aneurysm. Dysphagia developed, and later, symptoms of heart failure. At necropsy a very thin-walled saccular aneurysm was found, measuring 13 cm. from above down and 16 cm. from side to side, and arising by a neck 6 cm. in diameter from the ascending and transverse portions of the arch of the aorta.

CASE 3. A woman 28 years of age was admitted to the Essex County Hospital, Wanstead, on January 22, 1940. She had married 5 years before and 6 months later began to complain of palpitation and choking in the throat, which was made worse by excitement and relieved by sitting up. Three years after her marriage she became pregnant and had a normal delivery. For 15 months before admission she had had a gripping pain in the left submammary region. Her husband and child were healthy, her mother and sister were well and had had no miscarriages. Her Wassermann and Kahn tests were strongly positive, although the members of her family had negative tests. Cardioscopy showed considerable distension of the left ventricle and aneurysmal dilatation of the descending portion of the aortic arch and of the first moiety of the descending aorta. There was no visible dilatation of the ascending aorta. The heart was enlarged to the left. There was capillary pulsation of her lips and conspicuous arterial pulsation in the neck with a systolic thrill over the carotid and subclavian arteries.

Four cases of abdominal aneurysm. G. H. Jennings. *Lancet*, London, 1: 719-722, June 7, 1941.

The author reports here four cases of abdominal aneurysm. In the first two cases a syphilitic etiology was probable, and it was possible in the third. The varied symptoms were backache, sciatica, testicular pain, melena, constipation, abdominal cramps, suppression of urine, and symptoms of intestinal obstruction. The blood Wassermann reaction was positive in one case only. The course from diagnosis to death by retroperitoneal rupture was 9 days in the first case and about 10 weeks in the second and third cases. In each case, autopsy showed evidence of previous smaller bleedings and emphasized the liability of renal tracts to suffer from compression by these aneurysms. In two cases the aneurysm caused medial displacement of the ureter. Microscopic examination,

while showing in all cases marked lularity of the vessel coats with thinning of the media and thickening of the intima, supported a diagnosis of syphilis strongly in only the first case. In the other two cases the picture was too much complicated by arteriosclerotic changes to be diagnostic.

The author briefly reviews the literature on abdominal aneurysms. Osler thought that abdominal aneurysms were 10 times rarer than thoracic aneurysms. All writers who have described long series of cases (Nixon, Bryant, Kampmeier, and Osler) have agreed on the predominance of syphilitic cases, and only writers describing a few older cases (McNeely in 1937 and Jump and Leaman in 1938) have been impressed by arteriosclerosis as a causative factor. Many of the syphilitic patients were under 45. The comparative lack of support of the wall of the branching upper abdominal aorta is said to be responsible for the greater incidence of syphilitic aneurysms in the upper abdomen. Such aneurysms are usually saccular, while the arteriosclerotic aneurysms of the lower aorta are often fusiform.

The short history of such cases is noteworthy. From diagnosis to death the period is usually less than a year, although the aneurysm may develop over a period of years. Death is usually due to rupture and hemorrhage.

LABORATORY RESEARCH

The reactivity of the serum of malarial patients with spirochetal suspension
Harry Eagle, J. R. S. Mays, R. Hogan and L. E. Burney. *Am. Syph., Gonorr. & Ven. Dis., St. Louis* 25: 406-411, July 1941.

It is generally agreed that malarial infection may cause the appearance of positive Wassermann and flocculation

tests in the absence of syphilitic infection.

The complement fixation test using cultured spirochetes (Reiter strain) as antigen has been shown to be far more reliable in cases of leprosy than are the Wassermann and flocculation tests with malarial tissue extracts. The authors report here a study which shows that the spirochetal complement fixation test has been found to be so frequently positive in malarial and presumably nonsyphilitic patients that it apparently cannot be used for the serologic differentiation of malaria and syphilis.

Eleven patients who presented no clinical or serologic evidence of syphilis were inoculated with tertian malaria, either by the bite of an infected mosquito or by the intravenous injection of 5 to 10 cc. of whole malarial blood. At irregular intervals before and after inoculation and following the administration of quinine, blood specimens were collected and tested with (a) the complement fixation technic using a washed suspension of cultured spirochetes (Reiter and Kawan strains) as antigen, (b) Eagle microflocculation technic, and (c) the Eagle modification of the Wassermann technic. In 9 out of 11 patients one or more of the three serologic tests were positive or doubtful, the serum reactivity being confirmed by subsequent specimens in every case but one. Of a total of 127 specimens collected after the malarial inoculation, the Wassermann test was positive in 7 and doubtful in 5; the flocculation test was positive in 11 and doubtful in 6; while the spirochetal test was positive in 19 and doubtful in 16. Thus, the spirochetal test is of no value in the serologic differentiation of syphilis and malaria. This study suggests that the serologically active substances which appear during malarial infection, perhaps representing antibodies to the plasmodium, cross-react with these cultured spirochetes more strongly than they do with tissue lipoids. Only 4 specimens which were negative by the spirochetal test were positive or doubtful by the Wassermann or flocculation test. Twenty

specimens were positive or doubtful by the spirochetal test but were negative by the Wassermann and flocculation tests.

The frequency with which individual specimens gave discrepant results in the Wassermann, flocculation, and spirochetal complement fixation tests indicates the necessity for caution in the interpretation of conflicting or dubious serologic tests for syphilis observed for the first time during or immediately after some intercurrent infection.

On the reactivity of the serum and spinal fluid of leprous patients with spirochetal suspensions. Harry Eagle, Ralph B. Hogan, Charles F. Mohr and Samuel H. Black. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 397-405, July 1941.

The authors report the results of examining by means of the complement fixation test, using spirochetal suspensions (phenolized suspensions of killed Reiter strain of so-called *Treponema pallidum*), the serum and spinal fluid of 41 selected male lepers who had had a positive Eagle microflocculation serum test in the absence of clinical evidence or history of syphilis. Most of the patients were in the advanced stages of leprosy, and the majority had the mixed type of the disease. In this study, of the 41 serums retested, 4 were negative to the Wassermann, Eagle microflocculation, and spirochetal complement fixation reactions. These 4 were not considered further.

Of the remaining 37 serums, 12 were positive or doubtful only to the flocculation test; both the Wassermann and the spirochetal complement fixation tests were negative. Nineteen other serums were positive or doubtful by both the Wassermann and flocculation tests, the spirochetal test being negative. Only 6 of the 37 serums were positive to all three tests (Wassermann, flocculation, and spirochetal complement fixation).

There was a difference in the serologic reactivity of Wassermann-positive syphilitic and leprous serums, in that the leprous serums tended to give a dis-

proportionately high titer in the Wassermann as compared with the flocculation test. Of the 19 patients in this series in whom both tests were positive, the Wassermann titer was on the average seven times higher than the flocculation titer.

Of the six serums which reacted positively to the spirochetal antigen, three had disproportionately high Wassermann titers, with the spirochetal complement fixation tests barely positive. These three serums probably represent biologic false spirochetal reactions caused by leprosy. In the remaining three serums, however, relatively high titers were obtained in all three tests (Wassermann, flocculation, and spirochetal complement fixation), a serologic "pattern" approaching that observed in most syphilitic serums. The possibility must be considered, therefore, that these three patients were actually syphilitic.

A second group of 29 lepers giving negative Wassermann and flocculation tests was later included as a control group to be checked with the spirochetal complement fixation. Their spirochetal complement fixation tests were also negative.

Spinal fluids from nine of the leprosy patients with positive serum tests for syphilis (three of whom also gave positive spirochetal tests) were completely negative to all of the tests used.

It is possible only to speculate as to why patients with leprosy have false positive Wassermann or flocculation tests and why that reactivity does not usually extend to the spirochetal suspensions. According to the authors, the best working hypothesis as to the nature of the serum change in syphilis is that the patient elaborates antibodies to *Treponema pallidum* and that the reactivity of syphilitic serum with tissue extracts (Wassermann and flocculation tests) rests merely on the fact that these extracts contain a substance which happens to resemble one of the antigenic components of *T. pallidum*. Leprous patients also elaborate a serum factor which may also be an antibody to the causative agent. This serum reagin of leprosy

patients gives complement fixation (Wassermann) and flocculation with alcoholic extracts of mammalian tissue. However, the very fact that such serums do not usually cross-react with spirochetal suspensions to give complement fixation suggests that qualitatively different components of the tissue extract may be involved in the reaction with syphilitic and with leprosy serum. Attempts to separate these hypothetically different components of alcoholic beef heart extract are indicated.

The authors conclude that, in part, confirmation of the work of Cappelli, the use of the spirochetal complement fixation procedure makes it possible to identify as biologic false positive reactions most of the positive Wassermann and flocculation tests caused by leprosy in the apparent absence of syphilitic infection.

Studies on the role of *Spirochaeta pallida* in the Wassermann reaction. I. The relation of spirochetal antibodies to the Wassermann reagin. John J. Kolmer, Clara C. Kast and Elsa J. Lynch. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 412-434, July 1941.

According to Beck, spirochetes contain two antigens, one of which is apparently identical with the lipoids of alcoholic tissue extracts. According to Eagle and Hogan, either spirochetes contain two lipid antigens one of which is present in mammalian tissues, or else human syphilitic serum contains two antibodies both of which react with spirochetes but only one of which reacts with the lipoids of mammalian tissue.

Kolmer, Kast and Lynch report here the results of an investigation which showed that the absorption of human syphilitic serums with a cholesterolized alcoholic extract of beef heart (Kahn antigen) removed all antibody or reagin concerned in the Wassermann and flocculation tests but did not remove the complement fixing antibody for antigens in cultures of various strains of spirochetes including alleged cultures of *Spirochaeta pallida*. Absorption of human syphilitic serums with suspensions of spirochete

removed complement fixing antibody from them but not the antibody or reagin concerned in the Wassermann and flocculation reactions.

Absorption of a normal rabbit serum giving nonspecific positive Wassermann and Kline reactions with spirochetes (Reiter strain) did not remove the Wassermann antibody or reagin. Absorption of three normal rabbit serums giving positive complement fixation and agglutination reactions with an antigen of the Reiter strain, however, largely removed the natural antibody for them.

Agglutinins for various culture strains of alleged *Spirochaeta pallida* were found to be present in syphilitic and nonsyphilitic human serums in practically equal amounts. Especially large amounts were found in all serums for *Spirochaeta miodentium*. Syphilitic infection does not appreciably increase agglutinins for various strains of cultured spirochetes including alleged strains of *Spirochaeta pallida*.

Active immunization of rabbits with living and heat-killed vaccines of alleged cultures of *Spirochaeta pallida* and other spirochetes produced large amounts of agglutinin and complement fixing antibody for antigens of spirochetes but no antibody or reagin for Wassermann antigen. The agglutinins were fairly specific for homologous strains of spirochetes, but the complement fixation reactions were largely of a group character. Rabbits immunized with living and heat-killed vaccines of the Nichols-Hough strain of *Spirochaeta pallida* were not protected against syphilitic infection when inoculated intratesticularly and intracutaneously with homologous virulent *Spirochaeta pallida* (Nichols-Hough strain).

Tryptic digests of two strains of *Spirochaeta pallida* were antigenic in complement fixation tests with human syphilitic and rabbit antispirochetal serums. Precipitates obtained from tryptic digests after treatment with alcohol (F68 fractions) were also antigenic in complement fixation tests with human syphilitic and rabbit antispirochetal serums. The re-

sult may have been due to the presence of lipoids.

An alcoholic extract of the Reiter strain was antigenic in tests with human syphilitic serums, presumably due to the presence of lipoids. An antigen of the alcoholic extracted spirochetes was not antigenic in complement fixation tests with human syphilitic serums, presumably due to the absence of lipoids.

The authors' conclusions are as follows:

1. Very little, if any, agglutinin for alleged cultures of *Spirochaeta pallida* and other spirochetes is produced in syphilis above the amounts found in nonsyphilitic serums.

2. Complement fixation with antigens of cultured spirochetes, including alleged cultures of *Spirochaeta pallida*, by human syphilitic serums is largely due to a natural spirochetal antibody which may undergo some increase in syphilis, malaria, and leprosy.

3. Spirochetal antibody plays no role in the Wassermann and flocculation reactions.

Loss of virulence of *Treponema pallidum* in citrated blood at 5° C. Oscar Bloch, Jr. Bull. Johns Hopkins Hosp., Baltimore, 68: 412-415, May 1941.

Instances of transfusion syphilis have been recorded in which the donor was apparently in the incubation period of the disease. Such accidents are impossible to prevent by the usual clinical and serologic safeguards when direct or immediate indirect transfusion is employed. The use of fresh, whole or citrated blood is being rapidly replaced by the blood bank, in which citrated blood is stored at icebox temperature for periods of from 1 to 21 days before its use. Bloch has conducted experiments as to the survival time of *T. pallidum* in rabbit testis emulsion, when mixed in large amounts with citrated rabbit blood kept at blood bank temperature, 3° to 5° C.

It was demonstrated that, in fairly heavy suspension in citrated rabbit blood at 5° C., *T. pallidum* may survive for as long as 72 hours. Survival for 96 hours was not demonstrated. Bloch,

therefore, concluded that there is a definite risk of transmitting syphilis to the recipient of blood from patients with early syphilis if the blood has been preserved for 72 hours or less in the blood bank. Though this risk probably diminished rapidly after 96 hours, it would still be unwise to use the blood from persons with known early syphilis, since conclusions cannot be safely carried from one species of animal to another.

The accuracy of the determination of survival time may possibly be conditioned by an unpublished observation by Eagle that the addition of testicular tissue to a mixture of serum and *T. pallidum* increases the longevity of the organisms if the mixture is kept anaerobically, but may either prolong or shorten the survival time if the preparation is aerobic. In the present experiment it is probable that at least partially anaerobic conditions existed during the icebox storage period.

Effects of sobisminol solution orally in experimental syphilis. P. J. Hanzlik and W. Van Winkle, Jr. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 508-510, July 1941.

This is a final report on the effects of sobisminol solution in rabbits infected with *Treponema pallidum*, the drug being administered at the time of optimal development of the scrotal chancre. A total of 32 rabbits was used, of which 9 were untreated controls.

Fourteen rabbits voluntarily drank a 0.4-percent strength of sobisminol in water for from 6 to 63 days (median, 29 days). One cc. of this solution contained 2.8 mg. Bi (ion), prepared by diluting sobisminol solution. The average daily dose of bismuth was from 0.076 to 0.131 gm. per kg. of body weight (median, 0.091 gm.). The total dose of the drug ingested ranged from 0.74 to 6.27 gm. per kg. (median, 2.52 gm.). Treponemes disappeared from the lesions in from 3 to 14 days (median, 9 days) after the rabbits began to drink the sobisminol solution. Healing of the lesions was

complete in from 15 to 55 days (median, 25 days).

Lymph node transfers were positive in 4 of 12 treated rabbits. The actual daily excretion of bismuth ion ranged from 0.04 to 0.3 mg. (median, 0.1 mg.).

In the 9 control or untreated rabbits the results of the infection were as follows: Disappearance of treponemes from the lesions in from 14 to 70 days (median, 57 days); healing of the chancres in from 48 to 90 days (median, 77 days); positive lymph node transfer in all (5 of 5 rabbits) which survived. Thus, the voluntary drinking of sobisminol solution by rabbits promoted the clearing and healing of the scrotal lesion of experimental syphilis. These antisyphilitic effects compared favorably with those of other bismuth compounds used intramuscularly in rabbits.

Nine rabbits were given sobisminol solution gastrically with the aid of a suitable rubber catheter and attached glass bulb, using variable doses three times weekly for different periods of time. Two of these rabbits were given 0.02 gm. Bi per kg. of body weight (total 0.105 gm. in 1 week). Treponemes disappeared in 11 days and 14 days, and the chancres healed in 17 and 23 days. Three rabbits were each given 0.07 gm. per kg. (total 0.21 gm.) in 1 week. Treponemes disappeared in 9, 10, and 12 days, and the lesions in 2 rabbits healed in 33 days. The lesions of the third rabbit remained unhealed at the end of 16 days, when it died. Two rabbits were each given 0.035 gm. per kg. (total, 0.42 gm.) in 4 weeks. Treponemes disappeared in 6 and 12 days, and the lesions healed in 36 and 43 days. One rabbit was given 0.07 gm. per kg. (total, 0.63 gm.) in 3 weeks. Treponemes disappeared in 10 days, the lesion remaining unhealed at the end of 26 days when death occurred. One rabbit was given 0.07 gm. per kg. (total, 0.84 gm.) in 4 weeks. Treponemes disappeared in 10 days, and healing occurred in 40 days.

These results showed a fairly uniform tendency in the time for disappearance of treponemes in the majority of the

rabbits used (a median of 10 days after intrastatic administration of the drug). A similar uniformity occurred in the healing of the lesions in the 7 rabbits that survived (a median of 33 days). When compared with the same changes in the untreated controls, it is seen that the intrastatic administration of sobisminol caused definite spirocheticidal and healing effects in experimental syphilis (these results agreed with those of voluntary blood testing).

These observations were similar to the clinical antisyphilitic actions of sobisminol.

The relationship between the in vitro and the in vivo activity of sulfonamide compounds. H. J. White, A. Calvin Bratton, J. T. Litchfield, Jr., and E. K. Marshall, Jr. *J. Pharmacol. & Exper. Therap.*, Baltimore, 72: 112-122, May 1941.

A qualitative comparison of the in vitro and in vivo activity on β hemolytic streptococcus of 126 compounds consisting of sulfanilamide derivatives, sulfonamides, sulfones, sulfoxides, sulfides and certain miscellaneous compounds was made. It was shown (a) that no compound is active in vivo unless it is active in vitro or can be decomposed in the animal body to a compound which could be active in vitro, and (b) that compounds can be active in vitro but not active in vivo.

PUBLIC HEALTH ADMINISTRATION

Building morale in the United States Army and Navy. As described in a radio broadcast by three Government officials. *J. Social Hyg.*, New York, 27: 221-227, May 1941.

The work of building morale in the new citizen Army and in the Navy was recently set forth in a national broadcast

by three officials who are chiefly responsible for this important job—Frederick H. Osborn, Chairman of the Joint Army and Navy Committee on Welfare and Recreation; Charles P. Taft, Assistant Coordinator of Defense Activities in the Federal Security Agency; and Colonel William H. Draper, Jr., of the War Department General Staff. Mr. Osborn talked on the purposes of the work. Mr. Taft and Colonel Draper described specific problems, measures being taken, and the tangible benefits received. The talks were given through the National Radio Forum as arranged by the Washington Star, and they were broadcast over a national hookup of the National Broadcasting Company.

The Joint Army and Navy Committee on Welfare and Recreation has three functions: (1) To make available the advice of civilians who are experienced in special fields, so as to help the Army and Navy in planning facilities for the soldiers and sailors when they are off duty. (2) To act as a liaison between the Army, which is in charge of the camps; the Navy, which is in charge of the naval reservations; the Federal Security Agency, which supervises the work in the communities near the camps; and the public, which wants to help with voluntary services and contributions. (3) To help keep the public informed about what is being done for the soldier and sailor in his leisure time and how it relates to his training. This committee has a subcommittee of 17 educators headed by Clarence Dykstra, president of the University of Wisconsin. Charles Taft is chairman of the subcommittee on religious activities.

Blood testing of registrants for Selective Service. *J. M. A. Alabama*, Montgomery, 10: 436-437, June 1941.

Of 346,683 men between the ages of 21 and 35 who registered for Selective Service on October 16, 1940, in Alabama, 205,345 (59.2 percent) voluntarily presented themselves for a blood test for syphilis. Of the 186,470 specimens ex-

amined when this report was written, 16,447 (8.82 percent) were positive. These 16,447 men will be retested. Although the study is incomplete, it is believed that about 2 percent of the white men and 20 percent of the Negro men will have positive tests. A serious attempt is being made to get most of these men under treatment, and that this is occurring is shown by the trend in clinic population, which has increased by some 2,800 since the reports to counties have been made available. If the majority of the registrants with syphilis and their families and contacts who have syphilis are treated, a marked improvement in the syphilis problem should be apparent within the next few years.

The United States Public Health Service asked all States to make blood tests on Selective Service registrants on a voluntary basis. However, Alabama and North Carolina were the only two States who availed themselves of this opportunity to any appreciable degree.

In Alabama, the blood drawing for the tests was on a county basis. It was impossible to test each registrant in one day, since the laboratory facilities were insufficient. In 11 counties the registrants were offered the test on registration day, October 16, 1940. In the remaining 56 counties, the test was offered during the next 4 weeks.

Each county health officer was asked to arrange for enough centers to cover the county adequately. In each registration place a notice was prominently displayed stating the place, day, and time when blood would be drawn, and the registrars called the men's attention to these posters. Due to the excellent cooperation of the medical profession, all clinics were well-manned. Sufficient nurses, nurse-helpers (NYA girls and high school students), clerical assistants, and equipment were provided for each center. As each registrant presented himself at the clinic, the following data was obtained in triplicate: name, post office address, age, and color. By numbering the county, blood center, and patient, each person could be identified by number.

Blood was drawn by the syringe-needle technic, and sufficient syringes and needles were supplied to each county for the survey.

The blood was sent to one of the laboratories under the State system at the end of each day. A special shift W. P. A. workers, under the supervision of a trained laboratory technician, centrifuged and separated the serum from the blood. The following day the serum was frozen at a quick freezing plant. It was kept frozen by storage in either the quick freezing plant or in an ice plant until it could be tested by the laboratory since it was expected to take 4 to 6 months to complete the examinations.

The vice problem and defense. Basco Johnson. *Survey* Midmonthly, New York, 77: 141-143, May 1941.

Since September 1939, most of the effort to improve conditions by repressing prostitution in the areas near new Army camps and naval stations has been made by the American Social Hygiene Association, acting on request from the Army, Navy, and Federal Security Agency (including the U. S. Public Health Service). A bill (H. R. 2475), introduced by Chairman May of the House of Representatives Military Affairs Committee at the request of the Army, Navy, and American Social Hygiene Association, has reenacted Section 13 of the Draft Act of 1917. It provides that the Secretaries of War and Navy may set up zones of such radius as they deem necessary around military camps and naval stations, within which prostitution shall be a Federal offense, to be prosecuted only by the Department of Justice. Experience during the World War showed that such Federal legislation, judicially sustained by the U. S. Supreme Court, was effective in inducing sometimes reluctant State and local officers to enforce their own State laws. It was necessary to bring only a few cases into the Federal Courts. The published report of hearings on the present House Bill shows authoritative support from Federal, State, and local official and civic leaders.

The field work of the American Social Hygiene Association during the past 16 months has helped to demonstrate the value of law enforcement measures. To aid State and local governments in these efforts, the Federal Security Administrator, as coordinator of health, welfare, and related defense activities, has established Division of Legal and Social Protection (the Director of the Division is Bascom Johnson). The program of the Division will include studies (a) of the nature and extent of conditions favoring prostitution and sex delinquency in the neighborhood of Army and Navy camps, (b) of community needs and resources for remedying these conditions, (c) of problems created by the influx of young girls in search of employment or adventure, and (d) of the personnel and institutions available for temporary detention, classification, and referral to other agencies of women and girls who are in difficulty. Emphasis will be placed on providing protection, employment, or, when necessary, rehabilitation for women.

Such information will form a basis for cooperation with local communities and will strengthen the hands of officers in making such legal or administrative action as may be required. Where local resources are inadequate, recommendations will be made to the proper State or Federal authorities for aid.

Through programs conducted by the military and naval services, the case against exposure to venereal disease will be presented to enlisted personnel by chaplains and medical officers on religious, moral, and health grounds, and full information will be given on the use of prophylactic measures. The Division of Legal and Social Protection will undertake to make available sound factual information and the best scientific opinion on the sexual needs and problems of youth. The Division will have a staff which may total 80 persons, approximately half working in each of its two related fields—legal and social protection. The staff will be decentralized as far as possible, operating under supervisors in

the regional office under the Federal Coordinator. The supervisors will have their direct representatives stationed in various camp areas.

Every effort will be made to integrate these activities, not only at the Federal and State levels, but also in the local communities. Local committees, interested in legal and social protection, will be tied in with over-all committees interested in the whole program wherever they are established in the community. The objective is to avoid wasted effort, duplication, and overlapping, and—still more important—to provide a well-rounded program of community services.

Less is known about the problems of girls than about those of the soldiers. The protection of migrant girls is especially important. Some national provision comparable to the CCC camps may need to be devised.

An objective and constructive approach is being made to the problem of prostitution and venereal disease. Social and legal protection is an essential line of defense. But it must, and does, form part of a broader program through which wholesome recreation, decent housing, and all the other factors influencing individual and community welfare will also be maintained and strengthened.

Medical certificates to prostitutes. Editorial. Kentucky M. J., Bowling Green, 39: 156, May 1941.

It has been brought to the attention of the Kentucky State Department of Health that prostitutes are using, as an aid in solicitation, certificates signed by physicians which purport to show freedom from venereal disease. The practice of giving certificates which may assist prostitutes in solicitation is dangerous since the prostitute may show no sign of infection at the time of examination yet within a few days or even hours she may develop frank signs of venereal disease. The Kentucky State Department of Health regulations emphatically forbid the issuance of statements which may be used by prostitutes in solicitation. Physicians who find it necessary to give

their patients letters about their physical condition should write them in such a form that it would be impossible for prostitutes to use them in solicitation.

Private practitioner's role in syphilis control in Pennsylvania. John J. Shaw. *Pennsylvania M. J.*, Harrisburg, 44: 1224, July 1941.

In this letter to the editor, the author states that Pennsylvania is one of the few States which require a report on syphilis in the infectious stage as contrasted with syphilis that is not contagious. The regulation reads in part as follows:

1. Anyone suffering with syphilis, the duration of whose infection is less than 4 years, or who presents open syphilitic lesions of the skin or mucous membrane shall be considered as potentially endangering the public health, and it shall be the duty of this person to receive proper treatment for this infection.

2. Any physician who makes a diagnosis of syphilis as laid down in Paragraph 1 above shall make a report of such case direct to the Pennsylvania Department of Health, Harrisburg, Pa., by number without name and address.

3. It shall be the duty of the attending physician to report to the Pennsylvania Department of Health the name and address of any person who fails to report for treatment within a period of 2 weeks after the time designated unless the attending physician has knowledge of good and sufficient reason for delay.

During 1940, a total of 628 physicians reported that 1,471 patients with syphilis had come to them for treatment. During the same period, 420 patients were reported as delinquent in treatment in accordance with the regulations. Through the machinery of the State department of health, 313 of these delinquent patients were returned to the physician for treatment.

During the same period, the public clinics of the State reported that 11,173 patients had come to the clinics for treatment. This includes hospital clinics of the State almost without exception.

When this large number of patients who entered the free clinics of Pennsylvania in 1 year is compared with the number of patients whom private physicians reported as having come to the for treatment, it appears that the great majority of physicians did not comply with the regulation.

The regulation was designed with one thought only—that contagious syphilis be treated in order that the infection be stopped at the source. It is not the concern of a health department as to what may become of an individual who has syphilis in a stage that is not contagious or that is not liable to become contagious. On the other hand, it is the responsibility of a public health department to see it possible that syphilis is not carried from one person to another. Treatment that is properly administered to the syphilitic carrier whose infection is less than 4 years' duration is the means of stopping the spread of syphilis.

Syphilis is an endemic disease that has numerous foci of infection. Destroy the foci and the endemic ceases. Treatment of the infected individual is the only way that syphilis can be destroyed.

The cooperation of private physicians of Pennsylvania in reporting infectious syphilitic patients and those who become delinquent is earnestly requested.

Some practical results of physical examinations. A. J. Kammer. *Industrial Med.*, Chicago, 10: 230-233, June 1941.

Kammer deals with the practical results of physical examinations at one industrial clinic serving one plant—the examination clinic at the Indiana Harbor Works of the Inland Steel Co. He discusses syphilis among the specific conditions meriting special consideration. Of the first 15,000 different individuals consecutively examined, 8,085 were applicants for work and 6,915 were employees.

Over 300 employees were found to have syphilis (mostly latent), and they were referred to proper places for treatment. An effort was made to individualize their supervision and much time was devoted

to the reexamining, interviewing, and letter writing that go with good supervision. The workers are reporting to private physicians, to part-pay and charity clinics, and to medical school dispensaries scattered over the entire Chicago-Calumet area. It was possible to keep in touch with all cases and to exert constant pressure on them. The end-results cannot be evaluated for some time to come.

In considering the relative values of the different examination procedures, it was discovered upon review of 482 cases of syphilis diagnosed by repeatedly positive tests that only 11 men, or 2.28 percent of the total, gave histories of venereal infection. It was clear that direct questions pertaining to venereal disease might as well be dropped from the history form. Eighty-two men (17 percent) presented physical signs that aroused the examiner's suspicion of the presence of syphilis. By the serologic tests alone, 80.7 percent of the cases were discovered, and these cases would have been missed had not all men been subjected to serologic tests.

Eagleville High School class studies a State health problem. Health Briefs, Tennessee Department of Public Health, Nashville, 18: No. 4, pp. 2-3, Apr. 15, 1941.

The public school seems an ideal place to begin an educational program against venereal disease. One such plan was adopted by the Eagleville High School in 1940. This high school was one of eight schools designated by R. R. Vance, Tennessee State High School Supervisor, to include a unit study of the venereal diseases as communicable disease in the second semester curricula. The eight schools had faculties which included teachers who had received special training in health education.

Supervisor Vance suggested that the unit study be made in connection with biology or sociology classes. At the Eagleville High School the sociology in-

structor was also the member of the faculty who had taken the health training which qualified him to teach the course on venereal diseases.

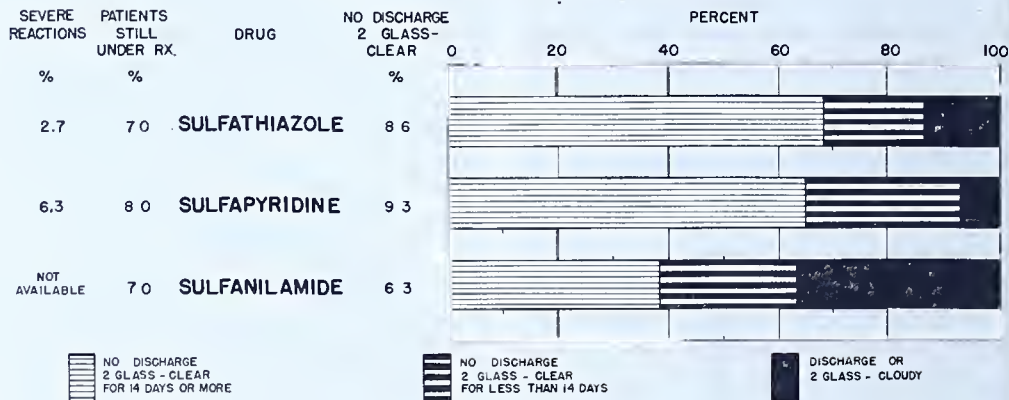
This sociology instructor explained to the sociology class, consisting of 11 girls and 2 boys, that the study of venereal diseases would be a unit of the class work and would not have value as an additional scholastic credit. Also, the course was to be a germ approach rather than a sex education approach to the subject. The students were eager to adopt the plan suggested. An explanation of the plan was sent to the superintendent of the Rutherford County Schools. He heartily endorsed the course and encouraged the class to continue. Each student talked with his parents and other relatives, and secured a statement from his family which he brought to class. Not one of the statements expressed opposition to the suggested plan, and several of the parents expressed interest.

About 8 weeks of class periods were devoted to the course, but most of the students continued to collect newspaper and magazine articles on the subject and to read informative books after the formal study was completed. Four main topics were used as an outline for the class work: (1) What are syphilis and gonorrhea? (2) History and prevalence. (3) Treatment. (4) Effects of untreated syphilis and gonorrhea.

Oral and written reports, posters, and lectures were alternately employed during the class periods in order that the meetings might be more interesting and that each student might be given an opportunity to make his contribution to the class. The public health department also furnished some slide pictures dealing with the effects of congenital syphilis and gonorrhea in connection with a home nursing course that was being offered the home economics class. The instructor of home economics included a brief study of the venereal diseases with the course in home nursing. The social science and home economics classes combined work during this period.

RAPID APPRAISAL OF SULFONAMIDE DRUGS IN THE TREATMENT OF GONORRHEA IN THE MALE MONTHLY REPORT

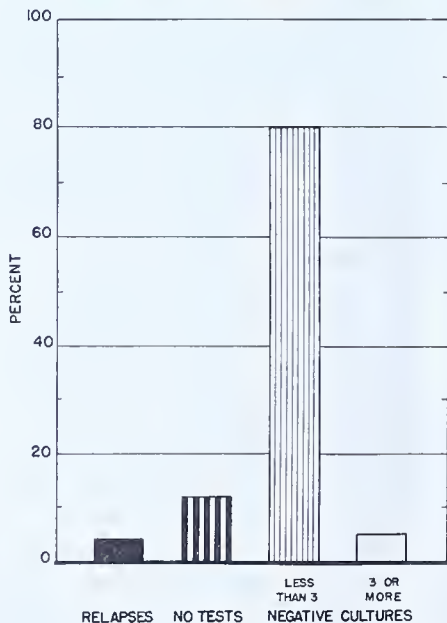
DISAPPEARANCE OF SYMPTOMS BY END OF FOURTH WEEK OF OBSERVATION



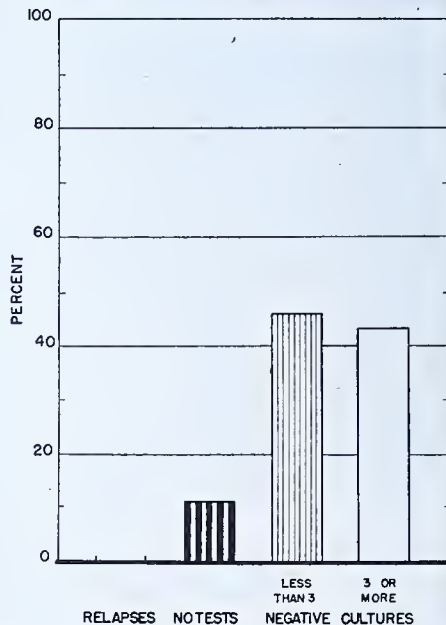
SULFATHIAZOLE

LABORATORY FOLLOW-UP IN INDICATED PERIODS ON PATIENTS SHOWING NO DISCHARGE AND CLEAR 2 GLASS TEST FOR 14 DAYS

STATUS AFTER TWO WEEKS FOLLOW-UP



STATUS AFTER THREE WEEKS FOLLOW-UP



NEW DRUGS

RAPID APPRAISAL REPORTS ARE PUBLISHED EACH MONTH ONLY FOR DRUGS IN GENERAL USE. RESULTS WITH NEW DRUGS INTRODUCED FOR CLINICAL EXPERIMENTATION ARE COMMUNICATED DIRECTLY TO THE RESEARCH CLINICS AND TO THE PHARMACEUTICAL LABORATORY MANUFACTURING THE DRUG. THIS INFORMATION IS AVAILABLE TO OTHERS UPON REQUEST.

Evaluation Studies as Indicators of Serologic Reliability

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THE GROWING interest in serologic evaluation studies should ultimately result in placing serology on a high level of accuracy. The splendid national serologic evaluations carried out in the United States since 1934 under the direction of the Committee on the Evaluation of Serodiagnostic Tests for Syphilis have apparently become an established institution. Recently, the number of State evaluations and even those of cities has been increasing by leaps and bounds. Unfortunately, some of these latter evaluations may prove misleading. The tendency appears to be to interpret them on the same basis as the more extensive national evaluations. Yet, these two types of evaluations belong in different categories.

State and city evaluations usually employ nonsyphilitic controls of such nature that practically any test performed in any laboratory would be expected to show a record of 100 percent specificity. This situation is bound to exert an important effect on the significance of these evaluation studies. It is axiomatic in serology that sensitivity, because it is not self limited, has to be limited by specificity. Therefore, when a 100 percent specificity record in an evaluation study is subject to question, the sensitivity results are necessarily questionable also.

Let us consider a hypothetical evaluation finding in which the standard Kahn test is compared with, let us say, test X. Both tests show 100 percent specificity. Test X shows 85 percent sensitivity and the Kahn test 75 percent sensitivity. We will then raise the question as to which is the more dependable. To throw light on this question it will be necessary to examine differences between the types of evaluation studies and the problem of

sensitivity and specificity in these studies and in actual practice.

DIFFERENCES BETWEEN EVALUATION STUDIES

Two basic types of evaluation studies may be defined as follows:

Type 1 determines which serologic test is superior to other tests.

Type 2 determines which serologic laboratory reports results below the level of average dependability.

Illustrations of the first type are the serologic conferences of the League of Nations Health Organization held in Copenhagen in 1928 and in Montevideo in 1930, and the study carried out by the Committee on the Evaluation of Serodiagnostic Tests for Syphilis in the United States in 1935. The latter committee includes leaders in the fields of syphilology, clinical pathology, and public health. The one thousand odd cases tested in each of these evaluation studies were chosen to correspond to cases, both syphilitic and nonsyphilitic, occurring in general practice. A good record of specificity and sensitivity in these evaluations is rightfully considered a distinctive achievement.

Illustrations of the second type of evaluation studies are those of limited scope, already referred to, which have become popular during the last few years. In the case of State and city evaluations, these are generally conducted by directors of the public health laboratories or by the venereal disease control officers. The nonsyphilitic cases are normal individuals and relatively few in number, and the syphilitic cases almost invariably have been treated. A good record of specificity and sensitivity in these evaluations is expected of all participating laboratories. If, for example, a laboratory reports a certain percentage of false posi-

tives in so small a normal group, it can be assumed that the laboratory does unreliable work.

RELATION BETWEEN SENSITIVITY AND SPECIFICITY IN THE TWO TYPES OF EVALUATION STUDIES

We will choose from the comprehensive evaluation study of 1935 two tests which reported more sensitive results than the standard Kahn test; for example, the Hinton and Eagle tests. In that evaluation study, it will be recalled, the controls included various pathologic cases as well as some normal individuals. The results taken from the published report¹ were as follows:

	Percentage of positive reports of syphilitic donors	Percentage of false positives ¹
Hinton.....	86.6	1.7
Eagle.....	84.1	1.1
Kahn.....	80.5	0.2

¹ Results obtained on a group of 468 presumably nonsyphilitic donors, including presumably normal persons and persons with tuberculosis, malignancies, fever and jaundice as well as pregnant women, menstruating women and women in the intermenstrual period.

It is evident that, with an increase in sensitivity of about 5 percent over the Kahn test, the Hinton and Eagle tests also showed an increase in false positives. But the more recent evaluation studies give a different picture. In these, a test which is 10 percent more sensitive than the standard Kahn test can yet give 100 percent specificity. I have in mind the presumptive test. The following results are taken from the official reports of the Committee on the Evaluation of Serodiagnostic Tests for Syphilis and were furnished by Senior Surgeon J. F. Mahoney, of the United States Public Health Service.

¹ The Evaluation of Serodiagnostic Tests for Syphilis in the United States. Supp. No. 1 to Ven. Dis. Inform., p. 21, U. S. Government Printing Office, Washington, 1935.

	Percentage sensitivity	Percentage specificity
Evaluation study 1938, 201 cases of syphilis; 96 normal persons: Control standard Kahn test.....	70.5	
Control presumptive Kahn test.....	79.9	
Evaluation study 1939, 217 cases of syphilis; 114 normal persons: Control standard Kahn test.....	77.4	
Control presumptive Kahn test.....	87.6	
Evaluation study 1940, 226 cases of syphilis; 111 normal persons: Control standard Kahn test.....	71.2	
Control presumptive Kahn test.....	83.0	

There is thus a discrepancy in the relationship between the sensitivity and the specificity in the 1935 and the 1938, 1939, and 1940 evaluation studies. In the 1935 instance, about 5 percent increased sensitivity over the standard Kahn test resulted in decreased specificity; while the other, as high as 10 percent increased sensitivity did not result in decreased specificity. The answer must lie in the kind of nonsyphilitic controls employed in these two types of evaluation studies.

SENSITIVITY AND SPECIFICITY IN HOSPITAL CASES

When a test which is about 10 percent more sensitive than the standard Kahn test, such as the presumptive test, is used in the routine admissions of a large hospital, it is found to be oversensitive. The department of syphilology at the University of Michigan Hospital has found that the presumptive test is positive in too large a number of cases in which the indications point to the absence of syphilis and considers this test unsafe for routine use.

It would appear that the results of the presumptive test in the 1938 to 1940 evaluations do not correspond to the results of the same test in routine hospital admissions. This lack of correspondence is undoubtedly due to the fact that hospital admissions represent unselected cases with but relatively small numbers of normal persons, while the controls in these evaluations consist of small numbers of normal persons only.

It must be remembered also that in these evaluation studies, the Committee has been obliged to take out certain questionable cases from the tabulations, presumably because they could not decide as to the presence or absence of syphilis in those cases. Such questionable cases are obviously not excluded from hospital admissions.

Briefly, the specificity results given by tests in routine hospital admissions correspond closely to the results of the 1934 evaluation study, but not to those of the more recent evaluations. I might add that the routine cases in the University of Michigan Hospital represent largely patients coming to the out-patient department. These patients are of the same type which one meets in private practice and whose blood specimens reach private and public health laboratories for serologic examinations. A test, therefore, which is too sensitive for routine use in hospital laboratory is also presumably too sensitive for routine use in other laboratories.

SENSITIVITY RATING IN THE MORE RECENT EVALUATION STUDIES

The sensitivity in the various evaluation studies, especially those carried out in State and city laboratories, as indicated, is based on the positive reactions obtained almost entirely in treated cases of syphilis. If the cases consisted largely of untreated secondary, tertiary, and other stages of syphilis and of patients inadequately treated, increased sensitivity would mean superiority. But with this type of cases frequently employed, increased sensitivity may not always mean superiority.

Let me cite the following incident which is a relatively common one. A syphilologist submitted a blood specimen for examination. We reported to him: Standard Kahn reaction Doubtful (\pm); presumptive reaction Positive ($++++$). He informed us that the serologic report of the standard test was in his opinion what should have been, the patient having had more than a year of intensive ther-

apy and the Kahn reaction having begun to show a decline some months back. The positive reaction given by the presumptive test did not disturb him because in his experience that test was oversensitive. Suppose the serum of this patient had been included in an evaluation study. The presumptive test would have been given the higher rating since it proved more sensitive in a case of syphilis. Yet, a syphilologist (who is professor of syphilology) interpreted the results of the diagnostic test as the more dependable.

Several weeks ago, another syphilologist told me that some time previously he had been asked to take charge of the syphilis clinic in the county hospital of his city, and one of his first administrative acts was to discontinue treatment of nearly half of the patients. Of these, some had been treated for more than 5 years and the others, for more than 3 years; all were past middle age. He did not consider any of these a menace to the public health, but he did consider continuing treatment to be a menace to the patient's health. Why had their treatment been so prolonged? Because of positive and, in many instances, doubtful serologic reactions. The reactions in these cases were obtained with the standard Kahn test. The number of these reactions would obviously have been increased by the use of tests having records of higher sensitivity in the recent evaluation studies.

Let me cite one more instance. A neurosyphilitic patient gave a positive spinal fluid reaction and a negative blood serum reaction. The patient was treated with malaria, and he began to give positive serum reactions. The verification test showed these serum reactions to be of the general biologic type and not of the syphilitic type. In due time, the serum reactions became negative. If the serum of this patient had been used in an evaluation study during the "positive" stage, that test which gave a negative reaction would have given an apparently correct serologic report, while the test giving a positive reaction would have been reporting a nonsyphilitic malarial reaction.

The impression gained from the sensitivity records of the recent evaluation studies may thus be questioned. A test which gives a sensitivity 10 percent higher than the standard Kahn test may actually be the less reliable test, and in certain treated cases the test of lower sensitivity may be the truer serologic indicator. What is particularly disturbing is to see evaluation reports in which the sensitivity of the Kahn test in other laboratories is higher than that obtained in this (control) laboratory. When our laboratory gives, for example, 75 percent sensitivity, and another laboratory 80 percent sensitivity, or higher, it means that either the other laboratory employs an incorrectly standardized antigen which is oversensitive or that it varies certain technical steps in such a way as to increase sensitivity. In the same evaluation study, the other laboratory may show 100 percent specificity, but in the cases which it is called upon to examine day by day, it is bound to give a proportionate increase in false positive reactions.

RECORDING SENSITIVITY AND SPECIFICITY IN EVALUATION STUDIES

We have seen that there are two distinct types of evaluation studies. The first type is extensive enough to justify sensitivity and specificity ratings of the participating tests. The second type is so limited in scope that all participating laboratories are, as a matter of course, expected to make a good record.

Unfortunately, the same method of recording the findings is employed in both types of evaluations. The result is that when one examines the tabulations of the less comprehensive evaluations, one notes that practically all laboratories report "100 percent specificity." This perfect specificity record tends to give laboratory directors a false sense of security as to their routine serologic work. It also gives them the false impression that the sensitivity of present-day serologic tests may be safely increased without affecting the specificity.

A possible solution to this problem is to use the terms "percentage sensitivity"

and "percentage specificity" only in the extensive evaluation studies, such as the one carried out in 1935. In the less extensive evaluations, if, let us say, 10 treated cases of syphilis and 100 normal controls are employed, the headings of the columns in the tabulations might read "Number of positives in 10 treated cases" and "Number of positives in 100 normal controls." If necessary, the treated cases should be grouped under "moderately treated" and "extensively treated." This method of recording results will be, in my opinion, more valid statistically and it will conform more closely to realities.

SHOULD DIAGNOSTIC SENSITIVITY BE INCREASED?

As a result of several local evaluation studies in which other tests showed high sensitivity than the standard Kahn test, my colleagues have brought up the question why I do not raise the sensitivity of the test "in conformity with the times." The fact is, it would be a simple matter to do so. All that would be necessary would be to use in the standard test the antigen now used in the presumptive test. An antigen of still greater sensitivity could then be used in the presumptive test. But no evidence is available that the standard Kahn test is insufficiently sensitive. The sensitivity results in the 1935 evaluation study corroborate this view. Excluding tests which gave more than 2 percent false positives, one finds that the different tests carried out by the respective authors showed an average sensitivity of 75.5 percent, while the standard

² It may be of interest in this connection to mention that the Bureau of Laboratories of the Michigan Department of Health, for about 15 years, has been sending to registered laboratories within the State five to six specimens for check examinations, several times a year. The laboratories of the Illinois Department of Public Health began the same practice in 1937. By employing, let us say, four syphilis serums and two nonsyphilitic serums for check purposes four times a year, these health departments keep in close touch with the interstate laboratories. No attempt is made to raise the participating laboratories on a percentage basis.

Kahn test showed a sensitivity of 80.5 percent.

What are the difficulties in raising sensitivity? 1. It is possible to raise serologic sensitivity to heights which are definitely beyond the range of syphilis. Thus, at this hospital, instead of obtaining the usual 3 to 4 percent positives with the standard Kahn test in the routine admissions, antigens of such sensitivity have been prepared that they may give as high as 40 percent positives in these admissions. Precisely to what level then should the sensitivity of the standard Kahn test be raised?

2. Even tests of conservative sensitivity give reactions outside of the realm of syphilis—namely, with serums of lower animals, with serums of cases of malaria and leprosy, and in isolated instances, of cases with other nonsyphilitic disturbances.

3. Vast numbers of cases diagnosed as syphilis are asymptomatic and the diagnosis is based solely on serologic tests. This fact would obviously necessitate a highly critical attitude in interpreting serologic tests. But to many physicians, a positive reaction means syphilis, and syphilis means treatment. Treatment, in turn, means the use of drugs not entirely free from toxicity. All this, aside from the distress a diagnosis of syphilis means to the patient.

4. The sensitivity of the standard Kahn test has been evaluated daily, since 1928, by an outstanding department of syphilology. According to staff members of that department, this test, far from being un-

dersensitive, if anything, is too sensitive. Is one to be guided by the results of these daily evaluations which yearly total approximately 35,000 tests (in which every patient giving a positive or doubtful Kahn reaction is referred to that department) or by an evaluation based on some 50 or 100 or 200 specimens?

CONCLUSIONS

1. Recent serologic evaluation studies carried out by State and city public health laboratory directors, within certain limits, give evidence of unreliable serologic results, thereby serving as a guide in improving upon such results.

2. The evaluation studies enable those in charge of private, hospital, and other laboratories to compare their results with those of a control laboratory.

3. Such studies, due to their limited scope, are but rough indicators of serologic reliability. They are not a gauge of correct specificity of a test, and a laboratory reporting "100 percent specificity" in an evaluation may actually report an undue number of false positive reactions in routine practice. Not being a gauge of specificity, the studies cannot be a gauge of correct sensitivity of a test.

4. Only by the more extensive evaluation studies, such as those carried out by the League of Nations Health Organization in 1928 and 1930, and by the American Committee on Evaluation of Serodiagnostic Tests for Syphilis in 1935, can the specificity and sensitivity of a test be gauged with a high degree of accuracy.

Persistence of a Positive Frei Reaction After Treatment of Venereal Lymphogranuloma With Sulfonamide Drugs

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HAS BEEN assumed that an individual who has developed a positive Frei reaction, due to an infection with the virus of venereal lymphogranuloma, will continue to yield a positive reaction for the remainder of his life independently of whether or not clinical cure has occurred.

Reports of the reversal of a positive Frei reaction are rare (1). Two hypotheses have been advanced to explain this retention of cutaneous hypersensitivity to inoculation of the inactivated virus of venereal lymphogranuloma. The first postulates the development of an irre-

versible immunologic condition and the second, the persistence of active virus in the presence of apparent complete arrest of the disease.

The demonstration that certain sulfonamide compounds have a curative effect upon experimental infection with venereal lymphogranuloma in animals (2, 3) and upon the acquired disease in man (4, 5, 6) has opened the way to a study of the latter hypothesis. Cure of venereal lymphogranuloma by the sulfonamide compounds is believed to result from the action of the defense forces of the body coupled with the virostatic effect of the drugs. There is no definite proof, however, that clinical cure of venereal lymphogranuloma with sulfonamide compounds is accompanied by complete inactivation of the virus.

The first reports of the effect of sulfanilamide upon the response to the Frei test have recently been made by Stein (7). In a series of 32 patients with the inguinal variety of venereal lymphogranuloma who had been successfully treated with sulfanilamide, Stein repeated the Frei tests on 5 of them 6 to 8 months after the original positive tests had been obtained. The second test was negative in 4 in whom the infection at the time of the first test was acute and of not more than 90 days' duration. The fifth patient, whose reaction was not reversed, had had the disease for 3 years. The amount and duration of treatment given to the 5 persons was not definitely stated but the cure of 26 acute cases in the series required, on an average, 83 gm. of sulfanilamide administered over a period of 18 days, or at the rate of approximately 140 gm. per month. Individual daily doses ranged from 4.0 gm. to 6.6 gm. Blood sulfanilamide levels varied from 2.0 to 16.0 mg. per 100 cc.

A study of the effect of sulfanilamide, neoprontosil, and sulfathiazole upon the

response to the Frei test in patients with venereal lymphogranuloma has been carried on in the venereal lymphogranuloma clinic of the New York Hospital for the past 2 years. The results of that work are presented here.

Between September 1938 and December 1940, sulfanilamide, neoprontosil, and sulfathiazole were exclusively and successively used in the treatment of 37 persons suffering from venereal lymphogranuloma. Sulfanilamide and neoprontosil were employed for the first half of the period and sulfathiazole since May 1940. Twenty persons received sulfanilamide alone, 6 sulfathiazole, and the remainder 2 or more of the drugs. One drug only was used at a time. Most of the patients were ambulant during the period of treatment. Five persons were hospitalized for treatment, and 2 of these did not require further therapy. Sulfanilamide alone was used during hospitalization according to the following plan: 7.2 gm. divided doses were given on the first day and followed by 5.4 gm. daily in divided doses for 1 to 3 weeks. The exact duration depended upon the tolerance of the patient for the drug. Ambulant persons received smaller doses of sulfanilamide as follows: For the first week 0.3 to 0.6 gm. was given 3 times daily. The dose was increased to 0.9 or 1.2 gm. 3 times daily at the beginning of the second week and this dosage was maintained for the next 4 or 5 weeks. The exact dose was governed by the reaction of the patient to the drug. Rest periods of 1 to 2 weeks were given on an average at 6 week intervals after which treatment was resumed, usually with a dose of 0.6 to 1.2 gm. 3 times daily. The total amount of sulfanilamide administered to any patient ranged from 16.8 to 584.1 gm.

Neoprontosil was given in doses ranging from 0.9 to 1.2 gm. daily. The drug was not used exclusively in the treatment of any of the 5 persons who received it nor was it taken with the same degree of regularity as were sulfanilamide and sulfathiazole. The total amount of neoprontosil given to any patient ranged from 6.3 to 255.6 gm.

From The New York Hospital and Department of Medicine, Cornell University Medical College, New York, N. Y.

Aided by a grant from the United States Public Health Service.

The dose of sulfathiazole was 1.5 gm. 3 times daily for 3 weeks followed by 4.0 gm. 3 times daily for 2 or 3 weeks. A rest period of 1 or 2 weeks then followed, after which the course of therapy was resumed, beginning with 1.5 gm. 3 times daily. The total amount of sulfathiazole received by any patient ranged from 10.5 to 338.0 gm.

The blood level of free sulfanilamide and free sulfathiazole was determined in 10 and 14 persons respectively. The figures ranged from 1.0 to 13.3 mg. per 100 cc. in the case of sulfanilamide and from 1.5 to 4.0 mg. with sulfathiazole. No serious toxic reactions to the drugs occurred in the group.

As a considerable amount of drug was often required to cause healing or marked improvement of lesions, the duration of treatment, including lapse and rest periods, was frequently long. It ranged from 13 days to 16½ months with an average of 7 months. Owing to the lack of uniformity of the lapse and rest periods among the individual patients, the most satisfactory expression of intensity of individual treatment appeared to be the amount of sulfonamide drug taken per month. This was obtained by dividing the total amount of the three sulfonamide drugs ingested by the number of months including lapse and rest periods, over which treatment was administered. The total amount of the sulfonamide drugs received by any patient ranged from 30.0 to 730.2 gm. The intensity of treatment was, with the exception of two cases, substantially lower than that employed by Stein and averaged 52.6 gm. of sulfonamide drug per month with limits of 4.4 and 143.3 gm. respectively.

The group consisted of 22 white males, 10 white females, 6 Negro males, and 7 Negro females. Thirty-three persons had the anorectal variety of the disease and the acute inguinal variety. One patient had a chronic cystitis with histologic findings in the bladder mucosa identical with those of venereal lymphogranuloma. The duration of the disease before the performance of the first Frei test was as

follows: 10 days to 3 months in 6 persons, 3 months to 1 year in 5, 1 year to 2 years in 6, 2 years to 4 years in 6, 4 years to 8 years in 8, 15 years to 35 years in 6.

Most of the Frei tests were performed with mouse-brain antigen and the remainder with yolk-sac antigen (8). The minimum diameter of the papule of a positive Frei reaction measures 7 mm. with mouse-brain antigen and 6 mm. with yolk-sac antigen. Doubtful reactions produced with these antigens are represented by papules measuring 7 x 6 mm. and 6 x 5 mm. respectively.

The interval between the performance of the first Frei test and the beginning of sulfonamide therapy was under 6 weeks in 23 persons, between 6 weeks and 12 months in 9, and between 1 year and 4 years in 5.

The interval between the performance of the second Frei test and the conclusion of sulfonamide therapy was as follows: 14 persons were tested upon the day treatment was completed, 8 within 4 weeks, 5 between 1 and 3 months, 7 between 3 months and 1 year, and 3 at 14 months after completion of therapy. Three persons had a third Frei test performed at intervals of 7 weeks, 3 months, and 12 months, respectively, after the performance of the second test.

The lesions in 17 persons were completely healed as the result of sulfonamide treatment. In addition, marked improvement occurred in 9 and improvement in 8; 3 were unimproved. The interval of time which elapsed between complete healing and the performance of the second Frei test was 1 day in 3 persons, between 1 day and 3 months in 6, between 3 and 9 months in 4, and between 12 and 19 months in 5.

RESULTS AND COMMENTS

Reversal of the Frei reaction from positive to negative did not occur in any case. In one patient, however, who had a lymphogranulomatous involvement of the bladder wall, there was a diminution in the degree of the response from positive to doubtful. The failure to obtain re-

versal of the reaction may have been due, in some instances, to the comparatively low intensity of therapy and, in others, to the chronicity of the disease prior to treatment.

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Gonococcal Infection in the Female

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SOME HAVE suggested that, since both diagnosis and determination of cure are difficult in the female, our main efforts toward eliminating gonococcal infections should be exerted in treating the male, reasoning that if all men are cured there would be no question of further female infections. To me the matter appears closely analogous to the problems raised in malaria control. In both instances the patient must be cured and also prevented from infecting an intermediate host. The intermediate host, be she a woman or a mosquito, must also be prevented from spreading infection. In the case of women, they must be cured and kept from continuing the chain of gonococcal infections. The destruction of the mosquito is simpler than its cure!

Although the treatment of gonococcal infections of men, women, and girls differs but little, diagnosis and determination of cure are often vastly more difficult in the case of the female than in the male.

Studies of the last 10 years have made it wise for us to forget much that was accepted as known fact before that time. We agree with Josh Billings—the immortal—who said, "It is better not to know so many things, than to know so many things that aren't so."

Ten years ago there was almost a superstitious fear of the dangerous possibilities of institutional epidemic contagion from single cases of gonococcal vaginitis of prepuberal girls. At the turn of the century Holt had reported a large number of cases of gonococcal vaginitis found in the wards of certain New York hospitals which had necessitated their temporary closure. Other epidemics of vaginitis in institutions were soon reported. Isolation technic in hospital care of patients was then but little understood or practiced. The diagnosis of gonococcal infections depended entirely on the microscopic examination of spreads, which we now recognize as a thoroughly unreliable procedure in all but acute infections of the female.

If possible, the treatment of gonococcal vaginitis of girls was even less satisfactory

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tory than its diagnosis. A host of anti-septic washes, applications to the vaginal surfaces, suppositories or pastes had for a day their supporters, but each was found inadequate. But little was known of the methods of spread from case to case, and it was almost believed that the gonococcus could flit about of its own volition infecting innocent girls with diabolic intent. Hospitals, schools, and child-caring institutions often would not admit children with even a past history of gonococcal infection. The question was frequently raised whether children with such infections were ever cured. With no adequate studies of groups of untreated control cases, these questions were difficult to answer positively.

Nine years ago the author of this paper became convinced that local treatments, such as applications and douches, could only be expected to destroy organisms on the surface of the vaginal mucosa. As the infection always lies deep in the mucosa and submucosa, it could not be affected by such forms of treatment. In their place estrin therapy was proposed. Girls treated with estrogens develop in a few days a tremendous thickening of the epithelial layer which covers the vaginal mucosa. At the same time the vaginal secretions change from near neutral to strongly acid (pH 4.5 to 5). In artificial media an acidity greater than pH 6 is fatal to the gonococcus. Children treated as just described usually showed marked clinical improvement in 2 weeks time. In 3 or 4 weeks, or even sooner, it became difficult or impossible to demonstrate gonococci in their vaginal spreads. Control by means of cultures, though attempted, was not successful at the time this form of treatment was introduced. The culture technic was then in its infancy. This method of treatment, I still believe, had advantages over the previous methods of local treatment. The introduction of a vaginal suppository did not upset the children under treatment as the forcibly given vaginal douches which preceded it had done. Clinical improvement following the use of estrogenic suppositories was sufficient to cause their wide-

spread adoption in the treatment of gonococcal vaginitis.

Unfortunately, treatment with estrogens is still employed. As I shall mention later, it has no curative value and is not to be compared with the brilliant results now obtainable with sulfathiazole. Some 3 years ago the New York City Department of Health with aid from Government funds organized a group of physicians to study the whole problem of gonorrheal vaginitis in girls. I have enjoyed my association with these investigators and will presently review some of the conclusions which seem justified by the study. Many of them have been published by Alfred Cohn and his associates. At the outset we aimed to find out as much as possible about the etiology, pathology, and prognosis of gonococcal infections in children and hoped to determine the best way of treating such infections, as well as studying the community problems that they involved. We believed that a study of the behavior of the gonococcus in the simple structure of the child's vagina might well throw light on its behavior in adult female infections.

It is generally believed that gonococcal infection of the vagina of the adult female is transient and uncommon during the years of estrogenic and menstrual activity. Before and after this era the epithelial layers of the vaginal mucosa are thin and few in number, and are highly susceptible to invasion by the gonococcus. In children the accessory glands of Skene and Bartholin are rarely involved. Gonococcal urethritis is common, but usually subsides in untreated cases before the vaginitis is cured.

Whether the glandular structures of the endocervix of the child are commonly involved, along with the infection of the vaginal mucosa, is still not positively known. In my own opinion, such infection is rare or does not occur. This is a difficult question to settle without an adequate number of autopsy investigations, and fortunately few children with gonococcal infections die, even from intercurrent disease. Infection of the por-

tio vaginalis, the extension of the vaginal mucosa into the cervical canal, is the rule and has been observed in several post mortem specimens. One does not see any evidence of mucopurulent discharge from the cervical glands, even in acute cases. This one would expect if such glands were the seat of an active infection. Tubal infection secondary to a gonococcal vaginitis is rare in the child (2 to 4 percent) and even before the days of sulfathiazole usually subsided rapidly with rest in bed. I have, however, seen three such little patients who died with pelvic abscesses.

The New York study² was based on 381 culture-positive cases taken from a total of 1,715 children with vaginitis who were examined. Of this culture-positive group 32.9 percent yielded negative spreads. The far greater reliability of cultures, as compared with spreads, was evident. The author has come to believe that spreads are rarely of any value in establishing a diagnosis of gonococcal infection of women or girls in any except acute cases where perfectly characteristic organisms are found in abundance. The possibility of error is too great when only a few shadow forms or poorly stained organisms are discovered. In the latter event opinions of experts are often at variance and a faulty conclusion is easily reached. About 45 percent of the children yielded positive rectal cultures while only a few yielded positive rectal spreads. None of them showed evidence of proctitis, and the rectal infection proved only transient. Occasional rare cases of severe gonorrheal proctitis have been observed elsewhere. In no instance in the children studied did a gonorrheal ophthalmitis result from the vaginal infection.

All of us were impressed by the fact that gonococcal infection of girls was not as prevalent as we had supposed. In 1939 only 316 such cases were reported to the Health Department in New York City.

² Further Observations on Gonococcal Vulvovaginitis. Cohn, A.; Steer, A.; Adler, E. L. Transactions of the Amer. Neisserian Medical Soc., June 1940, pp. 24-29.

In Baltimore during the same year only 136 cases were recorded.

A study of an untreated group of 4 girls used as controls was illuminating. In 78.8 percent of them spontaneous cure occurred in 25 weeks or less, as shown by cultures, spreads, and clinical appearance. The remainder, while clinically normal, continued to yield positive cultures on occasions, interspersed with negative laboratory results. These we considered to be latent infections with an indefinitely long duration. A similar situation is often encountered in cases of adult gonococcal endocervicitis. While some patients yielded positive cultures uncured, not a few were found with only occasional positive laboratory reports interspersed among frequent negative results during the course of their infection. In one instance only 2 positive laboratory reports were secured from a girl during an observation period of 13 months, although cultures and spreads were frequently made during that time. Had these children been examined in the ordinary clinic, or during a visit to a consultant for diagnosis, the likelihood is great that they would have been classified as cases of nonspecific vaginitis.

The specialist often finds himself in a dilemma when children with a long standing vaginitis are brought to him for diagnosis. It is necessary in every case of this kind to explore the vagina carefully to eliminate the possibility of a concealed foreign body as a possible cause of the vaginitis. The usual spreads and cultures for gonococci and other organisms should be taken. Vaginal secretion diluted with normal salt solution must be examined to eliminate a possible trichomonas infection. Cultures for Monilia yeasts, and Aspergillus infection are also indicated and are best made on Sabouraud's medium. If all these investigations prove negative, the possibility of a latent gonococcal infection, not shown by culture, still remains. If cultures cannot be repeated often, it is best under these circumstances to try the effect of a course of treatment with sulfathiazole. If any evidence of infection rapidly disappears

as a result of such therapy, one is entitled to believe that the case was probably one of latent gonococcal infection. Before trying such a therapeutic test, of course, every effort should be made to secure positive laboratory evidence of a gonococcal infection.

We turn now to the study of a group of children treated with estrogens. Many of us had long been concerned over the number of recurrences observed among children after an apparent cure by estrogenic therapy. At first we believed that reinfection explained this disappointing situation. The New York study group soon discovered that, although the children treated with estrogens improved clinically and spreads (which were the previous criteria of cure) frequently became negative, cultures often remained persistently positive. When cultures were used, it soon became apparent that real elimination of the gonococcal infection did not occur any more quickly or in any greater percentage of cases than in the group of children who received no treatment whatever. It is evident that the estrogenic treatment was but a palliative procedure which carried patients along until spontaneous recovery occurred.

With the use of sulfanilamide, about 90 percent of the girls treated were cured within 2 weeks.

Sulfapyridine in doses of $\frac{1}{2}$ grain per pound of body weight, not exceeding 2 g. per day for from 7 days to 10 days, given in 4 divided doses at 4 hour intervals rapidly cured 85 percent of a series of 89 cases.

Sulfathiazole given in the same manner is preferable to sulfapyridine because it is less toxic. The percentage of cures resulting is equal to the figure just given for sulfapyridine. None of the children treated showed evidence of toxic effects from the drug. Treatment with sulfathiazole is now the method of choice and is usually dramatically successful. Patients so treated should be followed for 3 months before being pronounced cured. Often it is difficult, or even impossible, to determine the source of infection in individual cases. In the past it was gen-

erally believed that if newborn female children were infected at birth, clinical evidence of such infection would appear within 2 or 3 weeks. It now seems possible, or even likely, that birth infection may be latent for months before the onset of symptoms. Different studies of infected children have shown that in a large percentage of such cases (probably 50 percent) a parent or other member of the family, also has gonorrhea.

Intensive study of a limited number of cases of gonococcal vaginitis by a psychiatrist convinced us that sex experimentation was frequent among infected children who were 6 years of age or older. Among them one child 8 years old gave a history of promiscuous intercourse with boys. Another 6 years of age was also found to have had intercourse. Rice, in a similar study made in Boston, found that 8 of a group of 15 girls with gonococcal vaginitis gave histories of sexual contact with boys or men. To us it seems likely that school infections are more apt to be acquired in this way than any other.

Nelson has long held the opinion that children with gonococcal infections should be excluded from school only as long as a free vaginal discharge persists. We are in full accord with this point of view. In one institution that came under the notice of Benson, a group of infected girls used the same toilets as an uninfected group for many months. None of the uninfected children developed vaginal or other infections. During the period of our study no epidemics of gonococcal vaginitis occurred in the schools of Greater New York, although children often attended their classes for many weeks before their infection was found or reported. None of us has ever seen a case of gonococcal vaginitis that could be proven to have its origin at the toilet. We believe that the practice of setting aside special hospital wards for children with gonococcal infections is unnecessary. Ordinary present-day isolation technique is sufficient to prevent cross infections from occurring.

The course of adult gonococcal infection parallels that of childhood infection

remarkably. Instead of a vaginitis, urethral and endocervical infections are of primary importance. The more serious upward extension to the tubes producing an acute, and later chronic, salpingitis is probably far less common than generally supposed. As a guess, I venture to say that not more than one infection out of six is followed by tubal infection. If the patient is under adequate treatment with sulfathiazole, such a sequel almost never occurs. The same rule holds true in the case of the male; i. e., a patient with an anterior urethritis under adequate treatment with sulfathiazole very rarely develops posterior urethritis, prostatitis, or epididymitis.

Our present conception of the course of gonococcal endocervicitis seems to stand in need of sweeping revision. In the past it has been taken for granted that the initial gonococcal infection ordinarily produced a red, swollen, acutely inflamed cervix accompanied by a free discharge of mucopurulent secretion—the textbook picture of acute endocervicitis. As the acute inflammatory phase subsided, the cervix, it was thought, necessarily remained enlarged and swollen, with granular or eroded areas about the os and a continuous mucopurulent discharge. The practitioner was led to believe that there was a typical picture characteristic of gonococcal cervical infection could he but recognize it.

We now realize that the acute inflammatory reaction, which we have been led to expect, is not a necessary prelude to chronic endocervical infection with the gonococcus. In fact, there is reason to believe that such a response at the onset of the infection is the exception, rather than the rule. Occasionally, as a result of public education, women now present themselves for examination at the office with the man responsible for their infection. Under such circumstances accurate data regarding the time of infection may be available. In such an instance, 10 days after exposure the author has seen a patient with an apparently normal cervix except for an excess of mucus secretion. Both spreads and cultures showed

gonococci in large numbers. In cases of chronic infection the experienced examiner can detect more often than the tyro some of the stigmata, such as evidences of infection of the cervix, thickening of the bases of the broad ligaments, indurated or tender tubes, eversion of the urethral mucosa or the telltale reddening of the orifices of the accessory glands. Sometimes even these evidences may not be apparent, and positive laboratory evidence may then come as a surprise. A carefully taken history may yield a valuable clue but is usually not helpful unless trouble and time have been taken to win the patient's confidence beforehand. Pelouze (Bull. New York Acad. Med. 17: 39-44, Jan. 1941) in discussing the treatment of gonorrhea in the male with sulfanilamide remarks that asymptomatic carriers, dismissed as cured, may transmit the infection to women, who in turn become asymptomatic carriers of the gonococcus. He adds that such a woman may again transmit the infection to still another man, who will develop a typical acute urethritis. The implication contained in this discussion is evidently that sulfanilamide treatment of the original patient has transformed the gonococcus so that the woman secondarily infected may become a latent carrier of the disease. My own interpretation of this situation is different. We are becoming aware that in many women gonococcal infection produces no striking inflammatory reaction. Such cases may well be regarded as latent carriers and are by no means rare. Pelouze's patients were probably not unusual, and the course of their infection was presumably uninfluenced by the sulfanilamide given to the men who were responsible for their infection.

Until now good standards of medical practice have required the demonstration of gonococci by laboratory methods before a positive diagnosis of gonorrhea was established. In recent acute infections of women and girls, positive spreads and cultures can ordinarily be secured and are rightly considered proof of the diagnosis. In some instances we have found

lowed untreated patients for as long as 6 months, while spreads and cultures remained positive. Sometimes only positive cultures are found while spreads early become negative. Usually after a few weeks or months it becomes impossible to find any positive laboratory evidence of infection, although gross inspection of the cervix assures us that infection is still present. Provocatives under such circumstances usually give us little or no assistance. It is probable that the invading gonococci lie in the submucosa, or in the depths of mucous glands which have been sealed. Earlier in this paper the case of a child was mentioned from whom in 13 months of investigation only two positive cultures were secured. We have seen not a few women with gonococcal endocervicitis with similar laboratory records. A much larger and more thorough study of prostitutes by Mahoney and his associates convinced them that it is impossible to secure laboratory evidence of gonococcal infection in a great majority of cases of long standing gonococcal endocervicitis. In his series of clinically infected prostitutes, only 21 percent gave positive cultures, while far fewer of them yielded positive spreads.

In my own considered opinion, spreads are only of real and great value in the diagnosis of gonococcal infection of girls or women during the acute phase of their infections. At this time if large numbers of characteristically formed, gram-negative intracellular diplococci are found, a positive diagnosis is justified. In the later stages of the disease I believe that a study of spreads is apt to be more misleading than helpful unless thoughtfully interpreted by a well-informed clinician. Too often a positive diagnosis has depended on the finding of a few poorly stained diplococci or organisms thought to resemble diplococci. I am satisfied to confess my own inability to identify gonococci with any certainty under such circumstances. I have seen many cases where errors in doing so have been responsible for most unfortunate situations.

Van Slyke in a recent meeting of the New York City Health Department re-

ported the results of an extraordinarily interesting study of the value of laboratory methods in the diagnosis of chronic gonococcal endocervicitis in women. Spreads were taken from the endocervix of 664 prostitutes who gave clinical evidence of infection. Three competent observers examined the same Gram-stained slides. One of them reported 160 as positive for gonococci, another found only 64 positives, and a third found only 44 of them positive. The microscopists by whom this study was made were all trained experts in this field of work. If these are the results under ideal conditions, can we have any confidence whatever in spread diagnosis of this type of case? Van Slyke further reported that in the same group of patients cultures were made by three excellent laboratories using the same preparations of media. Identical swabs from the cervix in peptone broth were used by all three laboratories. The results of the cultures in the three laboratories were in total agreement in only 75 percent of the culture-positive cases. In a further investigation Mahoney and his associates report that 1,598 prostitutes with presumable gonococcal infections were studied with repeated cultures. In only 21 percent was it possible to confirm the clinical diagnosis with cultures. In most sections of this country the use of cultures to detect gonococcal infections is, of course, not possible. The futility of taking spreads in rural areas with untrained personnel is well illustrated by the following observation. In a certain maternal health clinic in a southern rural community, serologic examinations for syphilis of pregnant patients was undertaken. Of 6,888 patients, 16.1 percent yielded positive reactions. It is fair to assume that in this group of patients gonococcal infections must have been frequent. Spreads were taken from the same group of patients and examined in laboratories of the State for gonococci. Of the entire lot, only 4 spreads were reported as positive. No comment is necessary!

In the New Haven City Clinic before the advent of sulfathiazole, the average

duration of observation and so-called treatment for women with gonococcal infections was 14.3 months before they were considered cured. Twenty percent of such patients became delinquent. During the past year this figure has been reduced to 10 percent. A group of 12 such patients on admission to the clinic gave positive laboratory evidence of gonococcal infection. They were kept under observation for periods ranging from 7 to 67 months. After the first few months, positive spreads could rarely be found. Cultures and spreads finally became entirely negative, but the clinical appearance of the cervix suggested latent infection. When treated with sulfathiazole the appearance of the cervix in every case rapidly improved or became normal. This again seems to show that infection often persists in spite of laboratory evidence to the contrary.

In the New Haven Hospital Gynecological Dispensary, an excellently run clinic with ample laboratory facilities near at hand, only four cases of gonococcal infection were found among a consecutive series of 2,500 gynecologic patients examined. Evidently many must have been overlooked.

Until now good practice, as previously mentioned, has demanded laboratory identification of the presence of the gonococcus before a diagnosis is made or reported. The facts just outlined convince me, and I hope the reader also, that we have been misled by our dependence on laboratory reports. Obviously the greater number of chronic gonococcal infections in women will remain unrecognized unless we radically alter our attitude. Obviously, also, the diagnosis must often be made with only the support of a carefully taken history and a painstaking pelvic examination backed by sound clinical judgment. Ordinarily the physician has refused to make a diagnosis of gonococcal infection without positive laboratory support lest he embroil himself in legal or other difficulties. He must, in the future, be encouraged to use careful clinical judgment and stand by it. Certainly in the past, before blood cultures and Widal reactions were

available, no physician hesitated to recognize and label cases of typhoid fever, even though many errors resulted. It is important that our city courts recognize a clinical diagnosis as sufficient to commit women for treatment. Demanding laboratory evidence or reliance on spread alone is a mistaken policy. I by no means suggest that we should omit every possible effort to secure positive laboratory evidence in cases of gonococcal infection in women, nor do I suggest that we return to the day when leukorrhea was considered sufficient evidence of such an infection. I do suggest that we recognize the fact that laboratory help is not available in the majority of cases of chronic gonococcal endocervicitis. I also suggest that spreads, as now generally used, are often misleading after the acute phase of an infection is passed, and that in chronic cases of infection of girls or women this laboratory procedure is rarely helpful and often misguides us. At best, and only when spreads have been examined by experts, positive or negative reports may be considered as supportive evidence in arriving at a diagnosis. Positive spreads even under such circumstances, should not be regarded as conclusive evidence of infection. Negative reports are, of course, valueless. The usual procedure in qualified laboratories is to render a report stating that gram-negative intracellular or extracellular diplococci morphologically resembling gonococci were, or were not found. Only too often this sort of report is interpreted as meaning "has (or has not) a gonococcal infection."

Rarely in cases of specific chronic endocervicitis after a series of negative findings one may suddenly encounter a spread which shows large numbers of gonococci which stain and are grouped as in an acute case. Here we are either dealing with a reinfection or possibly a sealed off focus may have discharged its contents. This is, however, an uncommon occurrence. Suspicious spreads may point the way to repeating cultures which have been negative. Ordinarily neither negative nor positive spreads are reliable evidence of infection or its absence in chronic

cases. When clinical judgment suggests the likelihood of a gonococcal infection, women and girls should be treated with sulfathiazole. If the responsible physician is unable to make even a clinical diagnosis with reasonable certainty, sulfathiazole treatment can be given without mentioning the possibility of gonorrhea to either the patient or the health authorities. The many pitfalls, difficulties, and errors in making clinical diagnoses without positive laboratory findings to support us, will be admitted by everyone familiar with this field of work. I do not mean here to minimize them.

In New Haven we have had³ adequate supplies of sulfathiazole since June 1940. Rapid cures have reduced the daily attendance of our city clinic by 50 percent. In both men and women we have used the dosage established by others—2 gm. per day in four doses, given for 12 days. In about 100 cases so treated no case of severe drug intoxication has developed. We believe that our rate of cure is about 85 percent or better. Reinfections, sometimes frankly admitted by patients, make an accurate calculation difficult. Patients with gonococcal infections who are pregnant respond well to treatment with sulfathiazole. Under such conditions sulfathiazole therapy is not harmful to either mother or child, and is urgently indicated. In his clinic at Fall River, E. L. Merritt, probably influenced by Hawthorne's "Scarlet Letter", makes it a practice to paint the genitalia and their surroundings of uncured patients with mercurochrome. His object in so doing is, of course, to present a warning sign to future candidates for infection. We plan to follow his example.

Physicians are rapidly becoming aware of the brilliant results obtainable with sulfathiazole therapy in the treatment of gonococcal infections. We believe that success in eliminating such infections depends at present on our willingness to recognize the limitations of laboratory procedures and particularly the fallacy of

relying on spread reports in chronic female infections. The need of a reliable diagnostic procedure, such as a complement reaction or skin test, is obvious. At present none such exists. Diagnosis in the majority of our cases among the female population must depend largely on the willingness of the physician to use sound clinical judgment and to act upon it.

DIAGNOSIS

The confusing multiplicity of serologic tests for syphilis. Standardization of the serologic report as a possible solution. Joseph Earle Moore and Harry Eagle. J. A. M. A., Chicago, 117: 243-247, July 26, 1941.

The ever increasing number of tests available for the serum diagnosis of syphilis and the necessity for interpreting conflicts between them, place a burden of evaluation on the physician. This he is often not qualified to assume since he may lack the necessary technical knowledge.

Although the standardization of serologic technic is not yet feasible, it is possible to standardize the method of reporting serologic results by the laboratory. In the interests of simplicity, clarity, and the best possible utilization of the laboratory data the authors make the following suggestions to the U. S. Public Health Service, to the American Society of Clinical Pathologists, and to author serologists for their serious consideration: They recommend that the proper names now used in reporting serologic tests be replaced by the generic term "Serologic Tests for Syphilis" (abbreviated "STS"), of which in routine practice there are the three categories of screen flocculation, standard flocculation, and complement fixation. They also recommend that the results of the laboratory findings, whether flocculation or complement fixation tests, single or multiple tests, be reported on an overall composite basis, as "Serologic Tests

³Through the courtesy of E. R. Squibb & Co. to the author.

for Syphilis—Positive, Doubtful, or Negative.”

The authors say that the onus of unifying conflicting laboratory findings is thus placed on the individual best qualified, the laboratory director. No information of diagnostic significance is withheld from the physician, for the reverse of the report sheet will carry a statement as to the results obtained with the individual tests on which the over-all report is based.

The Argyll-Robertson pupil. Ernest A. Spiegel. *Urol. & Cutan. Rev.*, St. Louis, 45: 428-432, July 1941.

The changes of the pupil described by Argyll Robertson in 1869 represent one of the most important clinical signs of a syphilitic infection of the central nervous system. It is necessary, however, to differentiate this syndrome from similar ones that have a rather different significance. The fully developed picture is particularly typical of tabes dorsalis or of general paresis combined with tabetic changes, while so-called cerebral syphilis usually produces absolute immobility of the pupil.

In considering differential diagnosis, the knowledge that the pupil contraction associated with convergence is normally somewhat more pronounced than the contraction on illumination should prevent a hasty diagnosis. In Adie's syndrome, there is a combination of tonic convergence reaction, apparent absence of direct and consensual light reaction, and absence of tendon reflexes. While the Argyll Robertson pupil is unilateral only exceptionally and is usually miotic, Adie's tonic pupil is frequently unilateral and is usually dilated. The convergence reaction in Adie's syndrome is tonic, and in Argyll Robertson is normal or hyperactive. The reaction to mydriatics, while poor in the Argyll Robertson pupil, is normal in Adie's.

The Argyll Robertson pupil may be simulated by an incomplete absolute immobility of the pupil. If cases of incomplete absolute immobility of the pupil are excluded, only on rare occasions is

the Argyll Robertson pupil found in non-syphilitic diseases. Cases resembling the Argyll Robertson pupil are not infrequently found in epidemic encephalitis affecting the vicinity of the aqueduct of Sylvius. Occasionally in chronic alcoholism, in diabetes, in lesions in the vicinity of the aqueduct due to trauma, tumor, malaria, and multiple sclerosis the pupil may present a similar picture. The pathogenesis of the Argyll Robertson pupil is discussed in detail on the basis of clinical, pathologic and experimental observations.

Relationship of race to the incidence of diphtheria and of positive Schick, tuberculin and Wassermann tests in hospitalized children. David W. Martin and Jay M. Arena. *North Carolina M. J.*, Winston-Salem, 2: 348, July 1941.

The statement often has been made that diphtheria is less frequently seen in Negro than in white children and that the reverse is true of tuberculosis and syphilis. In an attempt to answer this question, the incidence of diphtheria and the percentages of positive Schick, tuberculin, and Wassermann tests of the white and Negro children admitted to Duke Hospital from 1932 to 1939 were tabulated. Since these children were hospital patients, the figures may not be an accurate index, yet they are similar to the death rates in children from these diseases throughout the State.

The incidence of clinical diphtheria in the Negro children in this series is 69 percent of that in the white children and the susceptibility is 75 percent of that of the white children. The incidence of tuberculous infections in the white children was 37 percent of that in the Negro children. The incidence of syphilis in the white children was 13 percent of that in the Negro children, and the mortality in white children in the State is 11 percent of that in Negro children. The lower syphilis figures in the white children probably are due to a lower rate of exposure to syphilis, although a lower susceptibility also may be the cause.

The tabulation shows that, of 1,196 white children, 12 (1 percent) had positive Wassermann tests, and of the 496 Negro children there were 39 (7.8 percent). In the mortality statistics for North Carolina for 1938 (from birth to 14 years) there were 27 deaths from syphilis, or 1 per 100,000 population among the white children from 1 to 14 years of age, and 92 deaths among the Negro children, or 9.2 per 100,000 population.

Blood transfusion syphilis. Report of a case. Joseph C. Bulfamonte. Arch. Dermat. & Syph., Chicago, 44: 23-25, July 1941.

The patient, an unmarried woman 25 years of age who had typhoid fever, was given a transfusion of 400 cc. of blood which had been obtained from her brother. She was discharged from the hospital after 42 days. Six weeks later a generalized maculopapular rash developed. The Wassermann reaction of her blood at this time was strongly positive, but at the time of her transfusion her Kahn reaction had been negative. She was being treated for syphilis at the time of this report. Upon questioning, her brother said he had had a little sore on his penis which had appeared 1 week after intercourse. It had persisted for 1 month but had disappeared at the time of his giving the blood. His Kahn reaction had been negative just prior to the transfusion. Three to 7 days after the transfusion a rash developed on his body, and a positive Wassermann reaction was found. Two months later, even after treatment, the reaction was still strongly positive.

This man was probably in the seronegative primary stage of syphilis at the time his blood was first typed. It seems, therefore, that the results of laboratory tests do not constitute the only important factor in determining the compatibility of donors. Of paramount importance are the history and physical examination, and it is only by spending a few extra minutes along these lines that serious catastrophes can be averted.

Roentgenographic diagnosis of vertebral syphilis. Max Sgalitzer. Radiology, Syracuse, 37: 75-78, July 1941.

Three cases of syphilis of the spinal column are reported by the author from the clinic at the University of Istanbul. CASE 1 was that of a man who had had gradually increasing pain in the nape of the neck for 22 years. Drugs had afforded little relief from the pain and he had gone from doctor to doctor. The roentgenograms at the time of his admission to the clinic revealed, in addition to severe osteosclerosis and hyperostosis of the entire spine, extensive destruction of the bodies of the 3d, 4th, and 5th cervical vertebrae. There had been no collapse and no wedge formation of the vertebral bodies. The intervertebral disks were normal. A strongly positive Wassermann reaction was found. Antisyphilitic treatment was instituted (bismuth, arsenicals, iodides) and after more than 20 years of suffering the patient was relieved of his symptoms within a few weeks. There was no recurrence of pain after 1½ years.

CASE 2. A man, 36 years of age, had syphilis of the skull with widespread areas of bone destruction producing marked deformity. The neck was immovable and the nape strongly prominent. His Wassermann reaction was strongly positive. Beside the excessive syphilitic destruction of the cranium, there were syphilitic lesions in both humeri and the left ilium. X-ray examination of the cervical column revealed that the arch of the atlas was completely absent, only a narrow fragment of the body of the 2d cervical vertebra remained, and the ventral parts of the 3d, 4th and 5th cervical vertebrae were absent. There had been no collapse and no wedge formation because all had undergone osteosclerotic transformation. Energetic antisyphilitic treatment gave excellent results.

CASE 3. For 5 months this patient, a 37-year-old man, had suffered violent pains in the right shoulder radiating to the right arm. Roentgenogram examination of the cervical column showed de-

structive changes in the body of the 6th vertebra, and there was beginning sclerosis in the 5th and 7th cervical vertebrae. Both intervertebral disks of the 6th cervical vertebra were normal. The patient denied previous syphilitic infection, but his Wassermann test was strongly positive. A typical osteitis syphilitica was found in the diaphysis of the right humerus. Antisyphilitic therapy relieved the symptoms after 3 weeks.

In the differentiation of vertebral syphilis from vertebral tuberculosis it is seen that the tuberculous vertebra shows decalcified areas at an early stage; the body of the vertebra will often collapse under the weight of the body early in the course of the tuberculosis, and wedge formation will occur. Vertebral tuberculosis is close to the intervertebral disk while vertebral syphilis is chiefly in the ventral part of the vertebral body. Vertebral syphilis usually extends over a greater part of the vertebrae than tuberculosis. The differential diagnosis between vertebral syphilis and osteomyelitis is not difficult. Lymphogranulomatosis is distinguished by the decalcification of the vertebral bodies. Osteoplastic tumor metastases usually spread over more extended sections of the vertebral column than syphilis or may involve the entire spine.

The three cases discussed belong to the group spondylitis syphilitica destructiva, which chiefly involves the cervical spine. While this disease is not of frequent occurrence it may be more common than is generally believed, often being undiagnosed because its symptoms are not sufficiently known.

Prevalence of syphilis of the bones and joints. Report of a statistical study at the Hospital for Joint Diseases, with a review of the literature. Joseph Buchman and Herman S. Lieberman. *Arch. Dermat. & Syph.*, Chicago, 44: 1-12, July 1941.

A statistical study was made, covering a 10-year period ending December 31, 1938, of all known syphilitic persons admitted to the in-patient department of the Hospital for Joint Diseases and all

patients with syphilis registered in the syphilis clinic. In this total of 89,000 orthopedic patients, 119 persons were found who had lesions of the bones and joints due to congenital and acquired syphilis.

In 25 of the 119 cases syphilis was congenital and in 94 it was acquired. In the congenital group, there were 7 white and 9 Negro males and 2 white and 7 Negro females. The Wassermann reaction of the blood was positive in 22, and the only spinal fluid examined in this group showed a positive reaction although the reaction of the blood was negative. There was a positive reaction of the blood in the mother or the father or both for 16 of these patients, in 1 only the mother's blood was examined and was found to be negative; in the remaining 8 cases the parental blood was not examined.

In the group of 94 cases with acquired skeletal syphilitic lesions, 46 had Charcot joints, 19 periostitis, and 13 synovitis. There were 31 white and 24 Negro males and 18 white and 21 Negro females. The Wassermann reaction of the blood was positive for 57 patients, negative for 27, and not reported for 10. The Wassermann reaction of the spinal fluid was positive for 9 patients, negative for 10, and not reported for the remainder. Of these 94 patients, 38 gave a history of syphilis, 6 stated they had not had syphilis, and for 50 the history was not recorded.

A study of the literature on congenital syphilis indicates that (a) the frequency of congenital syphilis in newborn children is diminishing, (b) that lesions of the bones occur in a high proportion of syphilitic infants but tend to clear up rapidly after the child is 3 months of age, and (c) that the lesions are amenable to antisyphilitic therapy and rarely present orthopedic problems. The literature on acquired syphilis indicates that the high rates of incidence given for syphilis can refer only to small, selected groups, and that the high incidence of lesions of the bones and joints due to acquired syphilis refers to the older age groups, in which Charcot joints are pre-

dominant lesions. The authors, therefore, conclude that the dearth of cases, as shown in this study, is due to the relatively low frequency of syphilitic lesions of the bones and joints of orthopedic importance in persons with congenital and acquired syphilis.

Transient global aphasia and hallucinatory episode in neurosyphilis. Daniel Stats. J. Mount Sinai Hosp., New York, 8: 101-106, July-Aug. 1941.

The author reports the case of a 43-year-old Latvian-born man with neurosyphilis. Nineteen years before admission to the hospital he had a severe concussion of the brain in an airplane accident following which he was amaurotic for a short period of time and had frontal headaches. He became normal within a year and remained so until about 3 years before admission to the hospital. During the 3 years before admission he had frequent, increasingly severe, left supraorbital headaches which were relieved by rest. For 7 months before admission he had dyspnea on exertion and constrictive precordial pain radiating to the left arm, both relieved by rest. For the last 3 weeks of this period, he had left sacro-iliac pain radiating to the left shoulder.

Sixteen days before admission, he was awakened from a sound sleep by "electricity-like" pain in the left sacro-iliac region. This pain radiated up the torso to his head and disappeared in about 2 minutes. He could not move the entire right side of his body; he was unable to speak, and he had a right hemihypesthesia. The hemiplegia was of short duration. Three days later, he was able to use his right hand well. He knew what he wanted to write, but he could not put the symbols on paper. He had continuous loud buzzing in his right ear for a few days, but this gradually diminished in intensity and sounded like the ticking of a timepiece.

Twelve days before admission he noticed an inability to comprehend language symbols. About 4 days later, he had auditory hallucinations in his right ear,

limited to the languages of his youth—Latvian, Russian, and German. The voices were friendly and were those of his wife, aunt, or friends.

The next day he listened to radio music for the first time in about 10 days. He noticed a marked difference in tonal qualities. He was able to appreciate more fully the tonal variations and construction of a musical composition. He could discern more succinctly the function of each instrument in a major musical composition. Despite these changes with regard to the comprehension of music, he was unable at the same time to understand the meaning of spoken words.

At the time of admission to the hospital he still had some difficulty in carrying on a conversation. He occasionally used a wrong word and did not recognize the error. He was unable to understand some of the spoken questions. He made few mistakes when writing spontaneously, to dictation, or in copying.

The blood and spinal fluid Wassermann tests were 4 plus. The spinal fluid was under normal pressure. It was faintly xanthochromic. The Pandy reaction for globulin was 3 plus. There was a pleocytosis—88 cells per cubic millimeter, of which 3 were polymorphonuclear and 20 were mononuclear cells. The Lange colloidal gold reaction was 2222111000. There was 57 mg. percent total protein and 715 mg. percent chloride as sodium chloride. Roentgenograms showed a normal skull, a moderately dilated and hypertrophied heart, and a tortuous aorta.

When the patient was discharged from the hospital, 19 days after admission, all objective evidence of definite neurologic disease had disappeared, with the exception of the absence of ankle jerks and the presence of irregular pupils (the right was larger than the left). The patient was seen 3 months after discharge, at which time his aphasic and other difficulties were gone. He was receiving anti-syphilitic treatment.

The author was unable to determine the exact form of neurosyphilis in this case. The patient had a disturbance of cerebral function in the region of the

quadrilateral area of Marie. Meningo-vascular syphilis with involvement of the branches of the left middle cerebral artery was probably present. Additional observations are being made of the patient, and changes in his status are being recorded in an attempt to discover additional data which will permit an extension of the diagnosis.

On the evaluation of the clavicular symptom and the fifth finger sign in congenital syphilis. F. A. Oldach. *Deutsche med. Wchnschr.*, Leipzig, 67: 487-489, May 2, 1941.

The author examined 92 patients with a definite diagnosis of congenital syphilis (all of them seropositive and some of them with other manifestations) for the Higoumenakis sign of thickened sterno-clavicular junction and the du Bois sign of dystrophy of the middle phalanx of the fifth finger. The Higoumenakis sign was found in 5 of these patients and the du Bois sign in 3 of them. However, a positive du Bois sign was also found in 8 out of 123 control persons who were examined and who had no history or findings of congenital syphilis. The author concludes on the basis of his own observations that the Higoumenakis sign is a specific sign of congenital syphilis but that this cannot be said of the du Bois sign.

On congenital syphilis of the second and third generation. Dr. Janson. *Med. Welt.*, Berlin, 15: 483-484, May 10, 1941.

The author reports 2 cases of congenital syphilis occurring in the third generation. The first is the case of a 14-year-old boy who was seen by the author after he had been treated for 3 months for adenoids and "nervous exhaustion." Congenital syphilis was discovered, and all symptoms disappeared on antisyphilitic treatment. The serologic reactions became permanently negative after 2 courses of treatment. The patient's 22-year-old married sister was also found to have positive serologic reactions, as

well as the only child of this sister, 3-year-old girl. Neither the sister nor her child had manifestations of syphilis. The sister's husband had no signs of syphilis and his serologic reactions were repeatedly negative. The parents of the congenitally syphilitic siblings were not examined. The father was found to be nonsyphilitic, but the mother had positive serologic reactions; her sister also had positive serologic reactions. The mother's father was found to have tabes dorsalis with positive spinal fluid findings. His wife had a perforation of the palate and positive serologic reactions. She refused to have a spinal fluid examination.

The second case is that of a 52-year-old widow with gumma of the sternum associated with positive serologic reactions. She stated that her husband, who had been killed in 1915 in the war, had always been in good health. Her almost 80-year-old mother had positive serologic reactions for syphilis as well as syphilitic aortitis. The father of the patient had died at 40 years of age of heart disease. The patient's 30-year-old daughter had definitely positive serologic reactions; whereas a 26-year-old daughter had doubtful positive reactions. The husbands of these daughters had negative serologic reactions. Of the 3 children of the oldest daughter, the 2 oldest had positive serologic reactions, and of the 2 children of the youngest daughter the oldest child, aged 3 years, had positive serologic reactions.

Diagnostic methods in chronic ulcerative colitis. A critical analysis of procedures used in the differential diagnosis of the diarrheas and dysenteries. Moses Paulson. *Am. J. Clin. Pathol.* New York, 11: 588-604, July 1941.

Since indeterminate or chronic ulcerative colitis is a diagnosis reached after eliminating all of the recognized agents capable of producing a colitis, the diagnostic procedures involved are those employed in the diagnosis of all bowel disorders. These procedures are critically analyzed by the author. Details of technique are not given but references to sources

are made. Definitions are given to clarify the ambiguity of existing terminology.

According to the author, there is much striking experimental and clinical evidence that venereal lymphogranuloma, when associated with a colitis, is of pathogenic significance. The clinical picture of colitis associated with the virus of this disease is sometimes indistinguishable from that of nonspecific ulcerative colitis. The following methods should be used in the differential diagnosis:

1. The Frei test should be performed in all cases of obscure intestinal disorders. This test alone, however, is inadequate. A positive reaction establishes the fact that the reacting subject is or has been infected at some time during his life with this virus. It suggests the possibility of viral association with the colitis, but does not of itself prove that the virus of this disease is the cause of the colitis. A positive Frei test does not establish the presence of the virus in the intestine.

2. Bowel antigen offers a specific and more direct method of determining the presence of virus in intestinal tissue or discharge. This antigen is prepared from grossly fecal-free blood, mucus, and pus, or from involved tissue. The technic of intradermal inoculation and interpretations is identical with that of the Frei test, which should be done simultaneously or comparative purposes. Both the bowel antigen test and the Frei test should be done in all cases of indeterminate dysenteries. When there is a positive Frei reaction, the bowel antigen is a practical method of determining the connection between such a reaction and the etiology of the intestinal lesion. Even when the Frei reaction is negative, the virus may be present in the intestinal involvement. These are cases of anergy. By the use of bowel antigen these cases may be discovered more readily. A negative bowel antigen does not determine the absence of virus as conclusively as a positive antigen indicates its presence.

3. The neutralization test. Serum is mixed with the supernatant fluid of a centrifuged emulsion of mouse brain infected with the virus of venereal lympho-

granuloma. If the serum renders such a mixture uninfected when that mixture is inoculated intracerebrally into laboratory animals, then the serum possesses antibodies neutralizing the virus. The human source of such serum has, or has had the disease. This diagnostic method possesses the same limitations as the Frei test. Neutralization properties in serum will not be encountered among those having had the disease but who had failed to develop specific immune bodies (anergy).

4. Microscopic examination. This may be done when material is secured by excision at operation or at autopsy, or by biopsy from condylomata of the anogenital syndrome or from rectal stricture. The histopathology may be sufficiently characteristic to be diagnostic, or it may be that of nonspecific inflammation. In the former case, bowel antigen may be confirmatory. In the latter, it may prove to be diagnostic. In either case, the involved tissue may be prepared for animal inoculation.

5. Animal studies. The presence of the virus of venereal lymphogranuloma in suspected tissue or discharge is indicated after intracerebral inoculation in mice or monkeys by the following: The preparation of an antigen from the subsequently involved brain tissue which will result in a positive reaction when injected intradermally in those who have had the disease and who give a positive Frei reaction, rather than by the resulting meningoencephalitis of the laboratory animal which may not be specific.

Progress of medical science. Surgery.

Diseases of colon and rectum. Robert Turell. *Am. J. M. Sc.*, Philadelphia, 202: 282-305, Aug. 1941.

The author discusses (as venereal diseases of the colon and rectum) venereal lymphogranuloma, gonorrhea, chancroid, syphilis, Vincent's infection, and granuloma inguinale.

Venereal lymphogranuloma is a systemic disease with localized manifestations in the inguinal region, genital tract, and the anorectocolonic tube. The intestinal lesions consist of proctitis, colitis,

suppurations, fistulas in ano, rectovaginal fistulas, and stricture. The rectal strictures may be tubular or diaphragmatic in character. A positive Frei test usually establishes the diagnosis of the disease. The finding of the virus in the bowel discharges or tissues constitutes positive proof that the virus is the cause of the intestinal lesions. Sulfanilamide, sulfathiazole, or Frei antigen are effective therapeutic agents exerting profound beneficial systemic as well as local effects. To obtain the best results and the maximum of safety, especially during the intensive phase of treatment, chemotherapy should be instituted in a hospital. These patients, like those with other venereal diseases, are often unreliable, and it is dangerous to entrust potent drugs to them without proper daily medical supervision. Early toxic symptoms may go unrecognized, and they are unpredictable. Recently, intrarectal diathermy combined with Frei antigen has been proposed for the treatment of rectal stricture.

In men, anal gonorrhea is usually acquired through pederasty. Except for cases of anal intercourse, contamination in girls and women is believed to take place during the act of defecation when a simultaneous expulsion of gonococci-laden discharge from the vagina and a normal eversion of the anal mucous membrane occurs. Suitable biologic conditions for the acquisition and maintenance of gonorrheal infection are furnished by the transitional epithelium of the intermediate zone of the anal canal, the anal ducts, and the crypts of Morgagni. The infection may spread to the deeper perianal and perirectal structures through the anal ducts which lead to racemose and multiglandular structures located in perianal tissues, and penetrate the sphincter muscles, especially the internal sphincter. It is known that gonococci may remain alive and virulent for years in the anal structures and that reinfection of the genital tract may occur from the anal focus. Sulfanilamide, sulfapyridine, or sulfathiazole administered orally is effective in the treatment of anal

gonorrhea in the absence of localized suppurations or poorly draining sinuses.

Chancroid is found occasionally in the anorectum and is acquired by the direct inoculation of the streptobacillus *Ducrey* through pederasty, or, in the case of women, through contact with the penis through intercourse. The diagnosis can be made fairly readily by smear with the aid of the Unna-Pappenheim stain, and by the vaccine test which is a specific intracutaneous reaction comparable to the Frei test. Sulfanilamide or sulfathiazole are specific for this lesion.

In the infant, multiple superficial circumanal fissures or shallow ulcers are strongly suspicious of congenital syphilis. Infants may also have condylomata teeming with spirochetes, on the circumanal area. In the adult, a chancre may occur anywhere in the circumanal area but it is usually found in the posterior arc of the anal canal. A chancre occurring in the mucosa of the rectum has recently been reported. It may be acquired through pederasty, and in women by contact with the penis during sexual intercourse. Secondary syphilitic lesions comparable to mucous patches in the mouth apparently have not been observed in the rectum. Perianal condylomata containing numerous spirochetes have been found, as well as generalized maculopapular eruptions and multiple superficial circumanal fissures comparable to rhagades. Gummas, ulceration and stricture of the rectum caused by late syphilis have been found. Signs of central nervous system syphilis such as relaxation of anal sphincters and saddle-shaped perianal anesthesia have been noted. Antisyphilitic treatment should be instituted immediately after diagnosis is established.

Vincent's infection is caused by the symbiosis of fusiform bacilli and Vincent's spirillae. This lesion has been observed on the perineum or in the perianal region. Treatment consists of the topical application of a paste containing from 5 to 10 percent of arspenamine, neoarsphenamine, or mapharsen.

Granuloma inguinale is believed to occur in the anal and perianal areas. Recently a rare but apparently proved case of granuloma inguinale of the rectosigmoid with constriction and ulceration has been reported. This is regarded as a disease of the skin and subcutaneous tissues with late or no involvement of the lymphatics and lymph glands and is probably caused by the so-called Donovan bodies. These bodies are most frequently found in the tissues (or secretions) with the aid of Dieterle's silver stain. The material from the surfaces of ulcers may also be studied by smear stained by Wright's method. Tartar emetic administered intravenously or fuadin injected intramuscularly are specific for this lesion.

Lymphogranuloma venereum. Arthur W. Grace. Bull. New York Acad. Med., New York, 17: 627-646, Aug. 1941.

Statistics show that the number of new in-patient and out-patient cases of venereal lymphogranuloma admitted to the New York Hospital, 1934-40, has increased from a rate of 6 cases per 10,000 admissions to 10.8. Local manifestations occurred $2\frac{1}{2}$ times as frequently in the anorectal region as in the inguinal and about 5 times as often as in the genital region. In the anorectal variety there were 107 cases of stricture with proctitis, 10 cases of stricture without proctitis, and 10 cases of proctitis without stricture. Proctitis without stricture represents the earliest objective sign of anorectal lymphogranuloma. If the disease is recognized in this stage, complete and rapid cure can be obtained in over 75 percent of the cases. Colostomy was used in 19 cases out of the total of 128. Of 67 women with stricture, 62 had an accompanying proctitis.

In the inguinal variety, the primary lesion was present in only 14 of the 60 cases. The virus produced clinical manifestations in the affected nodes 7 to 21 days after coitus. In about four-fifths of the cases the disease was unilateral, in

the remainder bilateral. Frank pus appeared in the nodes in approximately three-fourths of the cases and, in the absence of treatment, broke through the overlying skin forming sinuses which persisted for months. In the 60 cases of the inguinal variety only 6 occurred in women.

There were primary lesions in 50 percent of the 28 cases of the genital variety. A concomitant chancroidal or syphilitic infection was sometimes found when there was an ulcerated primary lesion. Esthiomene was second in order of frequency of the genital lesions. Five cases of elephantiasis of the penis occurred in this series; 3 were the sequel of radical surgery, and 2 arose spontaneously.

There were 6 cases in which there was neither existing evidence nor past history of infection with the virus but which gave a positive Frei reaction. The marital partners of the 2 men and 1 woman whose contacts were traced presented active lesions. Consideration of the asymptomatic cases led the author to study the semen as a possible reservoir of the virus. He concluded that the virus of venereal lymphogranuloma is not present in measurable quantity in the semen and that infection is not transmitted by this secretion.

In discussing the systemic manifestations of the disease, Grace says that constitutional manifestations rarely accompanied the onset of the anorectal variety. As the disease progressed, however, there was a picture of chronic illness. After several years, arthritis developed in about 10 percent of the cases. Marked hyperproteinemia occurred in 42 patients with rectal stricture.

The cutaneous test discovered by Frei has proved to be highly specific and has been the sole means of accurate diagnosis until the recent work by Rake and his colleagues, who have employed lygranum antigen in a complement fixation test. Grace believes this new test will come to be regarded as the final court of appeal in determining lymphogranulomatous status.

Between July 1938 and May 1940, 31 ambulatory cases showing various manifestations of lymphogranuloma were treated with sulfanilamide at the New York Hospital. The drug was given orally, usually commencing with 0.3 gm. to 0.6 gm. 3 times daily and increasing to 0.9 to 1.2 gm. 3 times daily. Of the inguinal cases 80 percent were completely well within 3 to 6 weeks and the remainder within 16 weeks. In the anorectal cases, 39 percent were completely healed within 9 to 79 weeks, and 92 percent showed benefit from the treatment. Since May 1940, sulfathiazole has replaced sulfanilamide. Results, to date, show a slightly more rapid response than was found with sulfanilamide. This may be due to the fact that the amount of sulfathiazole administered has been almost double that given of sulfanilamide.

On photosensitivity in venereal lymphogranuloma. C. E. Sonck. *Acta dermat. venereol., Helsingfors*, vol. 22, supp. 6, pp. 499, 1941.

Sonck points out that in connection with venereal lymphogranuloma allergic manifestations frequently occur, such as inflammation of the joints and eyes, erythema nodosum, and skin eruptions resembling erythema multiforme, cases of which have been described in the literature. In this monograph the author calls attention to another allergic phenomenon, namely hypersensitivity to light which occurs in venereal lymphogranuloma but which has as yet received little attention from physicians and investigators.

Sonck's material consists of 400 cases, 200 men and 200 women, which are reported in detail. All of the patients had positive Frei reactions. In 140 of them eruptions due to photosensitivity occurred. The manifestations of the disease included subacute and chronic inguinal adenitis, chronic ulceration of the vulva or penis, chronic proctitis, and the genito-anorectal syndrome. Actinic dermatitis occurred in 60 percent of the chronic cases, in 30 percent of the subacute (inguinal)

cases in women, and in 12 percent these cases in men.

The following criteria are offered in the diagnosis of this type of dermatitis: The patient's history, the occurrence of the dermatitis at a mature age in a person who does not have a history of sensitivity to light, and the fact that the lesions occur only following exposure to the sun and that an exacerbation of the lesions on later exposure to heat, as in the steam bath, rarely occurs. The primary lesions consist of punctiform red papules and appear approximately $\frac{1}{2}$ to 3 hours after exposure to the sun and never later than the following morning. The lesions are often more or less itchy. They are localized to the exposed surfaces. On repeated exposure to the sun, as occurs in the summer, a certain amount of desensitization takes place. This sensitivity disappears when the original disease is cured.

The incubation period of the photosensitivity was determined in 20 cases. In these the eruption occurred 7 to 10 (usually 9 or 10) weeks after the infectious sexual exposure and about 4 to 8 weeks after the first lymph node symptoms.

Among the women with the chronic form of the disease joint involvement occurred concomitantly with photosensitivity in 33 percent of cases and in 19 percent of those who had no photosensitivity. Eye inflammation occurred in 19 percent of the photosensitized and in 7 percent of the nonphotosensitized patients; erythema nodosum occurred in 16 percent of the photosensitized and in only 4 percent of the nonphotosensitized patients. Markedly positive Frei reactions (3 plus or more) occurred in 32 percent of the photosensitized and in 9 percent of the nonphotosensitized patients.

No difference was found to exist between the photosensitive and the nonphotosensitive patients in regard to protein and lipid values of the blood serum. A simultaneous syphilitic infection also seemed to have no effect on this sensitivity to light.

TREATMENT

Recent experiences in the treatment of gonorrhoea in the male. R. M. B. MacKenna. Brit. M. J., London, 1: 958-961; June 28, 1941.

The author discusses the incidence of venereal disease and the part played by the Medical Services of the British Army in its prevention. He describes in detail an intensive method of treating gonorrhoea with sulfapyridine.

In military practice in England the incidence of venereal disease is low. The author believes that this fact is due to the enlightened policy of the Ministry of Health and the high standard of work which medical officers in charge of clinics have maintained during the past 20 years. In spite of the disturbances of war, the Medical Services have taken steps to insure that the prevention of venereal diseases and the treatment of these diseases are in keeping with modern standards.

The author states that the intensive treatment of gonorrhoea with sulfapyridine has been simple but successful. As soon as possible after the diagnosis has been confirmed by microscopic examination of the urethral discharge, the patient is put to bed. If he is considered to be a suitable subject for intensive therapy, he is given a milk diet, and mist, potassii citratiss and barley-water. He is given 2 grams of sulfapyridine in 48 hours. Treatment is not interrupted during the night. On the third day he gets up. He is usually a little weak and lethargic, but quite fit to eat in the dining room and go to the irrigation room for treatment. Usually his urethral discharge has almost stopped, but there may be a slight mucopurulent urethritis. Gonococci can seldom be demonstrated. He is then given irrigations of potassium permanganate (1:8000), or oxycyanide of mercury of the same strength. Treatment is given three times a day and the "grand lavage"

is used, the irrigating fluid being allowed to flow into the bladder. On the sixth day the patient, who has not urinated for at least 8 hours, reports at 6:30 a. m. for a "morning urethral smear." This is often not obtainable. Later in the day a 2-glass urine test is made, and if this is satisfactory a prostatic smear is taken. Usually no evidence of prostatic infection is found.

If these tests are favorable, the patient takes two bottles of stout with his evening meal, for alcohol is a good test of cure. The "morning smear" and the urine examination are repeated on the seventh day, and if these are satisfactory a provocative dose of gonococcal vaccine containing 300 million gonococci is given. On the eighth day the patient reports for another "morning smear"; a prostatic smear is taken and the usual urine test is made. If these tests are all satisfactory the anterior urethra is examined through a urethroscope. A diffuse reddening of the urethra is expected, but no lithritis, no inflamed follicles. A curved sound of suitable size is passed. The patient is kept under observation for an additional 2 days, as occasionally there is a delayed reaction to the vaccine.

All the patients treated have been hospitalized soldiers. Three weeks after treatment, the patient reports to a military hospital, where he is examined by a medical officer who has had training in the treatment of venereal disease. Various tests of cure are carried out at this time, and again during the following 2 weeks. Three months later he is again examined, and tests of cure are carried out. During the period of surveillance Wassermann tests are made to be sure that a concomitant infection with syphilis was not missed. The relapse rate among the patients treated in this manner is less than 5 percent.

Many hundreds of patients have been given this treatment. One patient died, but death was not due to treatment. Pyelonephritis with hematuria caused by the precipitation of acetylsulfapyridine crystals and sometimes with anuria persisting for as long as 40 hours occurred

in about 1 in 600 cases. In none of these cases has permanent renal damage been found. Some patients have taken magnesium sulfate and others have had eggs and onions while taking sulfapyridine without injury. Routinely, while undergoing the intensive treatment, the patient has only a milk diet. Prevention of constipation will usually prevent lumbar pain and hematuria. Nausea and vomiting can be reduced by not allowing the patient to smoke and by administering potassium citrate in large doses. The author considers it inadvisable to administer the treatment to patients who may have had gastric or duodenal ulcer, because of the danger of severe vomiting and possible hematemesis.

The effect of sulfonamides on mother and child when given shortly before birth. H. W. Kayser. *Klin. Wchnschr.*, Berlin, 20: 510-514, May 17, 1941.

At periods varying from 1 hour to 191 hours before birth the author administered sulfonamides, namely prontasil rubrum (10 patients), prontalbin (5 patients), albucid (10 patients) and eubasinum (10 patients) to 35 pregnant women. At birth the concentration of the drugs in the mother's blood and urine, in the amniotic fluid, in the umbilical cord blood, and later in the infant's urine was determined. Clinical observations were made on mother and infant. The sulfonamide concentration was determined according to the method of Kimmig. The dosage of each of the drugs administered was 3 gm., prontasil rubrum and prontalbin being given by mouth in 3 divided doses at hourly intervals and the other two drugs being administered each by means of a single intravenous injection. It was found that the placenta was impermeable to prontasil rubrum (azodyes) and that only the sulfanilamide which was split off passed into the blood of the infant and into the amniotic fluid. The other three drugs could be demonstrated in the amniotic fluid, in the infant's blood, and also, in most cases, in the infant's urine. The level of the in-

fant's blood was lower than that of the mother. There was a relationship between the amount in the amniotic fluid and the concentration in the infant's urine. No toxic effect of the above dosage of these drugs, either on the mother or the infant, could be demonstrated.

Evaluation of the use of sulfonamides in the treatment of gonorrhea. French R. Moore. *U. S. Nav. M. Bu. Washington*, 39: 386-391, July 1941.

The results of treatment of gonorrhea patients at the U. S. Naval Hospital, Pearl Harbor, are reviewed since August 1939. Sulfanilamide was used in 87 consecutive admissions from August 1939 to February 1940. Sulfapyridine was used from that date to August 1940 on 59 patients, and starting August 1940 sulfathiazole therapy was used, 80 cases being treated up to March 1, 1941.

The dosage of sulfanilamide was 60 grains daily for 2 or 3 days, 60 grains for 7 to 10 days and 40 grains for 8 to 10 days, the average total being 1,510 grains. Local treatment was also used. The discharge ceased in an average of 9.6 days. Treatment with sulfapyridine consisted of 60 grains daily, with an average total dosage of 930 grains. No local treatment was given. The discharge ceased in an average of 4.7 days. The daily dose of sulfathiazole was 60 grains, with an average total dosage of 805 grains per case. The average length of time until discharge ceased was 2.3 days. The percentages of cures were 59.8 for sulfanilamide, with 7 recurrences and 31 failures; for sulfapyridine 88.3 percent, with 2 failures and 5 recurrences; for sulfathiazole 91.3 percent, with 5 recurrences and 3 failures. These 5 recurrences have responded to a second course of therapy; the 2 failures had also failed to respond to courses with the other 2 drugs. The average time on the sick list was nearly 45 percent less with sulfathiazole than with sulfapyridine and 60 percent less than with sulfanilamide. There was one reaction following sulfathiazole, 15 following sulfapyridine, and 17 following sulfanilamide.

Blood counts on patients receiving sulfathiazole revealed no changes, while with sulfapyridine and sulfanilamide frequent blood studies were necessary. No relation was found between the blood concentration and the response made by the patient with either sulfapyridine or sulfathiazole.

Sulfathiazole, therefore, is considered much more satisfactory drug to use than either sulfanilamide or sulfapyridine for the treatment of gonorrhea.

Gonorrheal urethritis in the male.
Treatment with sulfapyridine and sulfathiazole. Charles A. W. Uhle, Leroy W. LaTowsky and Frank Knight. J. A. M. A., Chicago, 117: 247-249, July 26, 1941.

The authors further analyse the results, which have been published elsewhere, of the treatment of 87 patients with sulfapyridine and 55 with sulfathiazole. In the first group 92 percent were cured in an average of 51 days, with a range of 14 to 162 days; 96 percent were cured under sulfathiazole therapy in an average of 28 days, with a range of 7 to 3 days.

The average dose of both sulfapyridine and sulfathiazole in the 105 cases in which there was a cure was 3 gm. daily for 8 days, the average total dose of sulfapyridine being 23.5 gm., and of sulfathiazole 28 gm. However, the range of dosage for sulfapyridine was from 14 gm. to 111 gm. and for sulfathiazole from 12 gm. to 3 gm. In cases of refractory gonorrhea, the authors believe that two courses with rest period between are therapeutically better than a long-continued course and safer with respect to severe toxic reactions. Among the 87 patients receiving sulfapyridine, exfoliative dermatitis developed in 3 whose treatment was protracted. As a precaution against toxic reactions among the patients while they were at work, lower doses were given to clinic patients than to those who were hospitalized.

Reliance can no longer be placed on provocative tests as criteria of cure since more than 90 percent of the cases there

was no response to such tests despite the fact that smear and cultural studies still gave positive results. This study shows that cure should not be pronounced on the basis of the smear but of repeated sterile cultures, at least 3, obtained at intervals of 5 to 7 days.

The carrier state is defined as the time which elapses from the disappearance of symptoms of gonorrheal urethritis to the last culture of the prostatic fluid or urine containing secretions positive for the gonococcus. The carrier state for sulfapyridine was found to average 17.7 days, with a range of 2 to 50 days, while that for sulfathiazole averaged 17 days, with a range of 3 to 53 days.

In this series of patients, who were for the most part unintelligent persons, it was found that defaulting from treatment decreased in direct proportion to the time taken to explain to the patient what was desired to be accomplished. Among those treated with sulfapyridine 28.8 percent were defaulters, and among those treated with sulfathiazole (the second series) the defaulters were 9 percent.

Gonococcic conjunctivitis. A comparison of sulfanilamide, sulfapyridine and sulfathiazole in the treatment of one hundred and twenty cases. Philip Meriwether Lewis. J. A. M. A., Chicago, 117: 250-252, July 26, 1941.

Since June 1937 all patients with gonococcic ophthalmia in the isolation department of the John Gaston Hospital in Memphis have been treated with one of the sulfonamides, 90 having received sulfanilamide, 22 sulfapyridine, and 8 sulfathiazole. The usual dosage of sulfanilamide was $\frac{1}{3}$ to $\frac{1}{2}$ grain per pound of body weight as an initial dose, followed by a sufficient amount every 4 hours to bring the daily total to $\frac{1}{2}$ to $1\frac{1}{2}$ grains per pound (without counting the initial dose), continuing this dose for 5 or 6 days. Smaller doses of sulfapyridine were given, about $\frac{1}{3}$ grain per pound for adults and less than $\frac{1}{2}$ grain per pound for infants as the initial dose. The doses of sulfathiazole have been approximately the same as with sulfapyridine. It has

not been the practice to make determinations of the blood concentration. Since the absorption and excretion of sulfathiazole are more rapid than with the other two drugs, the daily dose should always be divided and administered every 3 or 4 hours in order to maintain the proper blood concentration.

Besides specific chemotherapy Lewis recommends local therapy—irrigation of the conjunctival sac every 4 hours with cool boric acid solution, instillation of 25 percent mild protein silver after the irrigation, ice compresses when there is considerable edema, and discontinuance of treatment when the eye is clean clinically and the smears are negative.

A comparison of results shows that in 50 cases having presulfonamide therapy there were 18 unsatisfactory results with an average of 20.3 days in hospital; in 90 cases with sulfanilamide there were 8 unsatisfactory results and 8.9 days; in 22 cases with sulfapyridine, 0 unsatisfactory results and 4.85 days; in 8 cases with sulfathiazole, 1 unsatisfactory result and 6 days. There was but 1 patient who had a severe reaction among the 120 patients, and he was given too large an amount of sulfanilamide. Nausea was rather frequent, especially from sulfapyridine. Serious blood changes were not encountered.

Lewis has found sulfapyridine amazingly effective in the treatment of gonococcal infections of the eye; sulfathiazole is somewhat less effective, but both are definitely superior to sulfanilamide. A cure may be expected within 3 days as a rule from the time sulfapyridine is begun.

From his experience with local treatment by sulfonamides he believes that it does not compare favorably with the internal use of the drugs. Recently a 5-percent solution of sodium sulfathiazole instilled locally every 2 hours has been tried along with the usual dose of sulfathiazole internally, and he believes it is of definite value. He believes that every patient with gonococcal conjunctivitis should immediately be given adequate systemic treatment with sulfapyridine or sulfathiazole.

Gonococcal conjunctivitis in children. A comparison of treatment with sulfanilamide and sulfapyridine, with note on sulfathiazole. Lewis K. Sweet. *J. Pediat.*, St. Louis, 19: 60-69, Jan. 1941.

Sweet reports his experience at the Gallinger Municipal Hospital in the treatment of gonorrheal conjunctivitis from July 1, 1938 to December 31, 1940. There were 26 patients treated with sulfanilamide, 29 with sulfapyridine, and 4 with both drugs. The groups were not treated concurrently, but they were relatively similar in race, sex, age, and size. Of the total number, 46 were newborn infants, of whom 12 (26 percent) were prematurely born. This suggests that the Credé prophylaxis may often be inadequately applied to very small infants. The 36 infants in this group who were born in the hospital constitute 0.75 percent of all infants born alive during the period of the study.

All these patients were isolated in a special room in the pediatric ward. They were kept in bed and given general supportive care. The eyes were irrigated with warm boric acid solution or a 0.5-percent solution of sulfanilamide frequently enough to keep the conjunctival sacs clear of discharge. A 10-percent solution of argyrol was instilled into the conjunctival sac several times a day, usually $\frac{1}{2}$ hour before the eye was irrigated. The chemotherapeutic agents were given immediately after diagnosis was established.

Both drugs were given in equal dosage which consisted of an initial dose of from 0.3 to 0.6 grain per pound of body weight followed by a daily maintenance dose of approximately 1.0 grain per pound of body weight. The maintenance dose was divided into 6 equal doses, given at 4-hour intervals. If the clinical response was not favorable the dosage was increased to 3 or even 5 grains per pound body weight per day. In a few cases a 5-percent solution of the sodium salt of sulfapyridine was given intravenously, and doses of 0.4 to 0.5 grain per pound body

eight were given every 6 to 12 hours as indicated. Patients who did not respond within 2 weeks of treatment were deemed failures. In all cases except in those which showed no response the administration of the drug was continued until the classical symptoms had subsided and smears were persistently negative.

There was a striking difference in the response to the two drugs. Of the 30 patients treated with sulfanilamide, 24 responded favorably, and of 29 treated with sulfapyridine primarily 28 responded favorably. Four of the 6 who did not respond to sulfanilamide were treated by sulfapyridine, with 3 showing good results. Therefore, of a total of 33 patients treated with sulfapyridine, 31 (94 percent) reacted favorably. There was no essential difference in the response of the patients who reacted favorably to the two drugs. Complications were very infrequent, corneal ulceration being encountered but once in the series. Evidence points to infection rather than sulfonamide toxemia as the cause of death of patients in the group.

In reviewing the literature the author found no reports of the use of sulfapyridine in gonorrheal ophthalmia in the United States, but there were 45 cases in the foreign literature.

Since January 1, 1941, 3 patients with gonorrheal conjunctivitis (10 years, 3 and 2 days old, respectively) have been treated with sulfathiazole. The dosage of sulfathiazole was the same as for sulfanilamide or sulfapyridine. In each instance there was remarkable improvement in the eye condition within 24 hours after therapy was begun. Sweet believes that sulfathiazole merits further trial.

Hospitalized male gonorrhea patients treated with sulfathiazole. J. R. Waugh. Hosp. News (processed), U. S. Pub. Health Serv., Washington, 8: 1-11, July 1, 1941.

There were 160 unselected hospitalized male gonorrhea patients in a series who were treated at the U. S. Marine Hospital, Norfolk, with 1.0 gram of sulfathiazole and 2.0 grams of sodium bicar-

bonate 4 times daily for 10 days, receiving a total of 40.0 grams of sulfathiazole. The apparent recovery rate for all patients was 79.0 percent, compared with a recovery rate of only 64 percent in a previous series of 473 patients treated with sulfanilamide. The apparent recovery rate for patients previously untreated was 88.5 percent, and for those previously treated with sulfanilamide or sulfapyridine only 62.5 percent.

There was no difference in recovery rate whether treatment with sulfathiazole was instituted during the first week of the disease or later. However, the longer the time which elapsed from the onset of the disease until treatment was begun with sulfathiazole, the greater was the likelihood that the patient had received previous treatment with sulfanilamide or sulfapyridine and was resistant to these compounds. Also, if the patient was sulfanilamide- or sulfapyridine-resistant, there was greater likelihood that he was also sulfathiazole-resistant.

There appeared to be no relationship between blood free sulfathiazole concentration and clinical response.

No complications such as epididymitis or arthritis developed in any patient after institution of treatment with sulfathiazole. It was unnecessary to discontinue treatment because of side reactions. Such reactions were mild and of no apparent importance in this series. In the previous series of patients treated with sulfanilamide it had been necessary to discontinue treatment because of reactions in 8 percent of the cases.

Waugh concludes that, in the treatment of male patients with gonorrhea, sulfathiazole is definitely superior to sulfanilamide both as to apparent recovery rate and low incidence of side reactions.

Chills and fever as a manifestation of sulfathiazole toxicity. William E. Molle and Walter Buck. Ohio State M. J., Columbus, 37: 752-753, Aug. 1941.

On reviewing the literature, the authors were unable to find a single case in which chills and fevers were specifically

reported as a manifestation of sulfathiazole toxicity.

They report the case of a 25-year-old woman who had chills and fever following the administration of sulfathiazole for right-sided pyelonephritis (pyelitis). The patient was given sulfathiazole on her third hospital day (15 grains every 6 hours). Soon after sulfathiazole therapy was begun, she began to have chills and fever. During a period of 4 days she had 9 chills, and her fever rose to a maximum of 105.8° F. At first, it was thought that she had a recurrence of the pyelonephritis, but examination of the urine revealed only 0 to 2 white blood cells per high power field, and there was no tenderness over either kidney area. The urine culture was positive for *B. coli* and alpha Streptococci. The patient complained of malaise, sore throat, generalized muscle aches and pains, and aching pain between her shoulder blades. She was nauseated and vomited frequently. The throat was slightly reddened, but there was no skin rash. The sulfathiazole was discontinued. On the day that the drug was discontinued, the patient had no chills and her temperature rose only to 100° F. The following day she felt and looked remarkably improved, she had no complaints, and she ate well. Her temperature remained normal. After 2½ days of normal temperature, she was again given sulfathiazole. After 12 hours had elapsed, and 3 gm. of the drug had been given, she again had chills and fever and recurrence of exactly the same symptoms noted during the previous episode. Twenty-four hours after the drug had been started the second time, she had a maculopapular eruption over the forehead, face, upper part of the thorax, arms, and legs. Itching was associated with this eruption. Twenty-four hours after the drug was discontinued the second time, the temperature and eruptions disappeared, and the patient was well enough to leave the hospital. She had not been exposed to direct sunlight.

Long has pointed out the following sequence of events which may aid in the differentiation of drug chills and fever

from chills and fever due to other causes: (1) There are usually 1 or more days of normal temperature before onset of chills and fever; (2) the onset is usually abrupt; (3) the chills and fever subside promptly with the discontinuance of the drug. According to the authors, the differential points are well illustrated in this case.

Nitritoid crisis following injection of tryparsamide. Heinz Lehmann, Canad. M. A. J., Montreal, 45: 121-130, Aug. 1941.

The patient, a West European male, 30 years of age, had received 2 courses of therapeutic malaria in 1936 in treatment of paresis. He afterward had 20 injections of tryparsamide and in 1937 was discharged as cured of his psychosis. In 1938 he had another 20 injections of tryparsamide and 10 injections of neosalvarsamine and bismuth. There was never any untoward reaction. In September, 1939, weekly tryparsamide injections were resumed. He had had 2 injections without any sign of intolerance, but during the third injection, which was being administered intravenously very slowly, the patient suddenly complained of dizziness and severe pain in the abdomen and chest. His neck and face showed marked flush, the conjunctivas were reddened, and the pulse was bounding. Ephedrin was administered. The subjective and objective symptoms disappeared gradually. In about 5 minutes he collapsed while still lying down; suddenly lost consciousness and an epileptiform convulsion occurred. Artificial respiration was resorted to and 7 cc. of coramine was injected. Afterward, the picture suggesting heart failure, 400 cc. of blood were withdrawn. Respiration and pulse improved and 2 hours later he was completely awake. He then had a chill followed by a slight rise in temperature. He was kept in the hospital 48 hours and then discharged, showing no abnormality of his cardiovascular system and normal neurologic findings. He has remained well up to the present time and no further convulsions have occurred.

Lehmann says he is inclined to believe that the organic damage which the areis inflicted on this patient's central nervous system lowered his convulsive threshold so that vasomotor disturbances elicited an epileptiform fit in his case, though they might have passed without any specific effect in a nonparetic.

While it is very rare to see a nitritoid crisis with tryparsamide every physician administering the drug should be aware of the possibility that it might occur.

Treatment of syphilis in pregnancy. A comparison of arsenicals. Frederic R. Minnich. *Am. J. Obst. & Gynec.*, St. Louis, 42: 159-161, July 1941.

In September 1938, at the colored division of Grady Hospital, Atlanta, it was decided to compare the use of mapharsen with that of neoarsphenamine in the treatment of congenital syphilis. All the patients studied were Negroes, each prospective mother had had a positive Wassermann or Kahn serologic test for syphilis, and each had had at least 10 treatments (some as much as 27) with either drug at weekly intervals during the course of her pregnancy. The weekly dosage of neoarsphenamine was 0.45 gm. and of mapharsen it varied from 0.03 gm. in the first part of the study to 0.05 gm. in the latter part, no patient having received 0.03 gm. for all 10 treatments.

Among the 155 patients treated with mapharsen, 80.64 percent had full term live babies, 15.48 percent premature alive, and 3.88 percent born dead or dying in the hospital. Among the 116 treated with neoarsphenamine, 87.07 percent had full term live babies, 8.62 percent premature alive, and 4.31 percent born dead or dying in the hospital. In the mapharsen series 93 percent and in the neoarsphenamine series 38.79 percent showed negative blood tests at labor. There were 2 sets of twins in the mapharsen series and 1 set in the neoarsphenamine series.

Of the live babies in the mapharsen series 57.14 percent were examined in a follow-up study, and in the neoarsphenamine series, 58.18 percent. In the former, 44 percent of those followed up (4.08 percent of the total) were proved to be

syphilitic and in the latter the percentages were 7.81 and 4.54. X-ray studies of the long bones were made on all of the babies that were born dead or that died in the hospital. Only 2 had any signs of congenital syphilis; in 1 case the mother had received only 5 doses of 0.03 gm. of mapharsen and in the second, 3 doses. There were no severe reactions, immediate or delayed, in either series. The only notable difference in the toxic reactions was that nausea following the administration of mapharsen did not seem to be as frequent or as severe as with neoarsphenamine.

Peroral bismuth as initial therapy in syphilis. Adrien Lambert. *Union méd. du Canada*, Montreal, 70: 502-503, May 1941.

From March to July 1940, 6 patients with seronegative primary syphilis and 2 with secondary syphilis were treated by means of sobisminol. They received an average of 6 capsules of sobisminol per day (1.2 gm. of bismuth) over a period of nearly 4 months. No other antisyphilitic drug was administered. None of these patients had gastro-intestinal or renal disturbances while taking the drug.

In spite of the fact that the patients with primary seronegative syphilis received large doses of bismuth (9 capsules per day) the Wassermann reaction in 5 of them became positive under treatment. In 4 of them secondary lesions developed in spite of this treatment.

The author explains the inefficacy of bismuth given perorally by saying that bismuth in itself has no treponemocidal action but that protein-bismuth compounds, which are formed when the drug comes in contact with the tissue and especially with the blood proteins, do have this action. He concludes that bismuth perorally should not be used alone in the treatment of primary and secondary syphilis.

On the treatment of phagedenic chancre. O. K. Scholl. *Dermat. Wehnschr.*, Berlin, 112: 393-394, May 17, 1941.

The author reports the case of a 46-year-old man who was first seen when

he presented a lentil-sized chancre of the sulcus coronarius, associated with regional lymphadenopathy. Because of the induration of the lesion and the history of the patient's exposure to a prostitute 12 days previously, the author instituted antisyphilitic treatment consisting of neoarsphenamine in a dosage of 0.45 gm. and bismogenol 1.0. The blood test was negative at this time. Three days later, however, the patient was alarmed because the lesion had markedly increased in size and had a necrotic center. The patient was given prontosil in a dosage of 2 tablets 3 times a day, and on the following day the lesion was cauterized with 10 percent silver nitrate solution followed by the application of iron chloride solution and finally by the application of ammoniated mercury ointment. Two days later—after the administration of 18 prontosil tablets and 2 doses each of neoarsphenamine and bismogenol—the lesion was smaller and cleaner. Prontosil was discontinued 10 days later, and about 1 month later the lesion was epithelized. The Wassermann, Sachs-Georgi, and Kahn tests at this time were negative.

The author attributes the main therapeutic effect to prontosil in this case, although he states that the local treatment no doubt had a favorable effect by preventing the spread of the necrotic process. He advises the use of prontosil in this type of lesion.

PATHOLOGY

Anatomic findings in the heart in combined hypertension and syphilis.

Chauncey I. Royster, James R. Lisa and John Carroll. *Arch. Path.*, Chicago, 32: 64-75, July 1941.

The anatomic findings of the heart in 33 cases of cardiac failure occurring in association with combined chronic hypertension and syphilis without aortic regurgitation are presented. The material studied was obtained from 33 cases in which autopsies were made at City Hos-

pital, Welfare Island, New York, between 1928 and 1939.

The hypertensive patients with syphilis after cardiac failure supervened presented a clinical picture and course strikingly similar to that of patients with syphilitic aortic regurgitation and failure. The first type of patient responded poorly to therapy and had a bad prognosis. The condition occurred more frequently among males than among females. In 22 cases the ages were between 40 and 55 years, and 19 of the patients were Negroes. The Wassermann reactions of blood serum or spinal fluid were positive in 21 cases.

Death was due to cardiac failure alone in half the cases and to cardiac failure with added factors of partial or complete renal failure or infection in the remainder. The arteriosclerosis of the coronary arteries was much more severe than that found in members of the same age group who had hypertension not complicated by syphilis. Hypertrophy tended to be extreme. The damage to the myocardial fibers was severe and extensive and included diverse pathologic processes.

Syphilitic myocarditis was found in 11 instances. Extensive rheumatic myocarditis was present in 6 cases, in 2 without valvular involvement. Other lesions included massive infarction with or without coronary occlusion, acute and chronic interstitial myocarditis, acute endocarditis, acute miliary infarctions, acute myocardial necroses, and acute abscesses. The role of infection, valvular or extracardiac, in the production of myocardial damage appeared of special importance. The presence of severe coronary sclerosis associated with chronic hypertension and constitutional syphilis appeared to render the myocardial fibers more susceptible to injury, such as that produced by specific infection, as syphilis or rheumatic fever, or a nonspecific pyogenic infection. The clinical syndrome of cardiac failure was associated with extensive demonstrable injury to the myocardium in almost all cases. The demonstration of myocardial damage depends on adequate histologic examination.

The present series and the cases reviewed from the literature have extensive myocardial damage as a feature in common. In most of the cases it was associated with congestive failure or sudden death due to cardiac disease. There is frequently seen at necropsy an extraordinary amount of myocardial damage unassociated with clinical findings regarded as indicative of cardiac dysfunction. The authors recognize that the heart has extraordinary ability to function in spite of severe damage and thus may present only minor signs, which are easily overlooked or undervalued.

Case of syphilitic heart disease. Case Records of Massachusetts General Hospital. Tracy B. Mallory, Editor. *New England J. Med.*, Boston, 225: 155-159, July 24, 1941.

This is the case record of a 47-year-old laborer who died in the hospital. A post mortem examination showed dissecting aneurysm of the aorta, with rupture into the pericardium, media necrosis aortica, syphilitic aortitis, cardiac hypertrophy, chronic rheumatic endocarditis with aortic stenosis.

The clinical diagnosis had been coronary thrombosis, syphilitic and hypertensive heart disease, syphilitic aortitis, and aortic regurgitation.

At the age of 23 years, this patient had had a penile chancre.

About 17 months before his first admission to hospital he (a known syphilitic) presented himself to the out-patient department for advice regarding the performance of manual labor. He had signs of syphilitic heart disease, his Hinton test was positive, a spinal fluid Wassermann test was positive. His blood pressure was 205/105. Antisyphilitic treatment was administered and he was allowed to do light work. He remained well without signs of heart failure. His blood pressure ranged between 205/140 and 105/90. Six weeks before his first admission, he had a cold in his chest, with a dry cough that finally produced small amounts of thick yellow sputum. On the day of his first admission he suddenly began to

cough up small amounts of bright red blood every 2 or 3 minutes until he had raised about 1½ cupfuls. There were no accompanying symptoms and no pain. The patient was in the hospital 2 weeks. He had no more hemoptysis during his hospital stay. On the fifth hospital day a roentgenogram showed a line of increased density perpendicular to the diaphragm in the medial portion of the right lower lung field, with a wedge-shaped area of consolidation close to it, apparently far posteriorly. No fluid was seen in the pleural cavity. Two weeks after admission a roentgenogram of the chest showed that the area of dullness had completely disappeared. The patient was discharged.

On admission to hospital 2 years later, his blood Hinton test was still positive (although treatment had been kept up for 2 years) and his blood pressure was about 190/100. A roentgenogram taken 8 months before showed that the heart had increased slightly in size since the previous examination, the enlargement being in the left ventricle. A to-and-fro murmur over the aortic area and down the left border of the sternum was noted frequently, as well as an apical diastolic blow. Three hours before his second admission, after a meal, the patient had a sudden, severe, nonradiating substernal pain, which was constant and still present on admission. Nausea and vomiting followed, with rapid cyanosis and cold, clammy extremities. He was orthopneic. The blood pressure was 60/0, the pulse barely discernible (rate 90 per minute). The heart sounds were of fair quality, with occasional extrasystoles and a diastolic murmur along the left sternal border. The heart was enlarged, the apex being in the anterior axillary line. There was no peripheral edema. An electrocardiogram showed a normal rhythm, with a rate of 90 and a P-R interval of 0.15 second. There was a depressed take-off in ST₁ and ST₂, with a prominent T₁ and T₂. T₃ was upright, and R₄ low, with a depressed take-off in ST₄.

The patient died 8 hours after admission, without change in his physical signs.

LABORATORY RESEARCH

Contribution to Hilgermann's spirochetal vaccine. Reply to the report of R. Hilgermann, 1941, No. 6. K. Zieler. Dermat. Wehnschr., Leipzig, 112: 345-349, May 3, 1941.

The author discusses at length the work of Neuber and Hilgermann on the controversial subject whether Hilgermann's vaccine consists of true syphilis spirochetes or whether it is a nonspecific vaccine. The author considers it to be a nonspecific vaccine because proof that it consists of *Spirochaetae pallidae* is still lacking. He quotes the conclusions of Albrecht, who carried out fundamental and careful animal experiments, as follows: "Neither by direct transmission experiments nor by lymph node transfer, nor by means of superinfection were we able to furnish proof that the spirochete cultures of Hilgermann used in the investigation contain syphilis spirochetes pathogenic for animals." The author concludes by stating that if Hilgermann does not consider Albrecht's results conclusive, he should submit a "virulent" spirochete culture to the State Institute for Experimental Therapy at Frankfurt am Main where it can be studied by experienced but impartial investigators.

Concluding reply to the preceding discussion of K. Zieler. R. Hilgermann. Dermat. Wehnschr., Leipzig, 112: 349-350, May 3, 1941.

Hilgermann states that the view of Zieler according to which nonpathogenic antigen does not produce protective substances is incorrect. Nonpathogenic antigens can undoubtedly stimulate the diseased organism to produce protective substances. This is the essential object of vaccine therapy. The tests of virulence or avirulence in the animal experiment represent something entirely different

from the stimulation of animal or human cells for the formation of antibodies.

In answer to Zieler's criticism (*M. Klin.*, No. 3, p. 60, 1941) that the cure obtained by Hilgermann in tabes represent spontaneous remissions, Hilgermann replies that it is remarkable that so many of these so-called remissions occurred in the groups of patients treated with the vaccine. He also states that the serologic reversal in tabes and congenital syphilis is to be attributed to the treatment with this specific vaccine.

Hilgermann further states that if Albrecht at the Serotherapeutic Institute Frankfurt am Main has so much experience in the field of experimental syphilis then it should have been easy for him to transform Hilgermann's avirulent strains into virulent strains by culturing them in a phosphorus-free atmosphere. Hilgermann however does not furnish proof here that he himself has cultured these virulent strains from his avirulent strains.

The treatment of 'syphilitic infection with *Spirochaeta-pallida* vaccine.

Hilgermann. *Med. Klin.*, Berlin, 360-61, Jan. 17, 1941.

The author briefly reviews the literature in regard to the favorable therapeutic results obtained by various authors by means of Hilgermann's spirochetal vaccine. This vaccine consists, according to the author's description, of a suspension of a *pallida* culture 4 to 6 weeks old which has been rendered avirulent by growing it in the presence of phosphorus.

Two cases of tabes, 2 of congenital syphilis, and 1 of acquired syphilis which were treated by means of this vaccine are here reported. Vaccine injections were given every 10 days to every 3 or 4 weeks, the patients receiving 8 to 13 injections. Complete remission was obtained in both cases of tabes. The Wassermann reaction in both cases of congenital syphilis as well as in the case of acquired syphilis became negative following this treatment. Vaccine therapy was

ollowed by treatment with arsphenamine and bismuth in the cases of tabes, the other patients having received a considerable amount of this type of therapy before vaccine treatment was resorted to and which had produced little effect.

Hilgermann concludes that whenever antisyphilitic drugs and fever therapy do not cure the infection, vaccine therapy is indicated, because it stimulates the formation of immune bodies and thus brings about cure. He believes it is also possible that spirochetal vaccine treatment early in the course of a syphilitic infection will increase the resistance of the body and thus make the usual antisyphilitic drugs more effective.

Methods used in the differentiation of culture-spirochetes. A further contribution to Hilgermann's spirochetal vaccine. B. Albrecht. *Dermat. Wehnschr.*, Leipzig, 112: 351-355, May 3, 1941.

At the request of the editors, Albrecht offers this report on the modern methods and criteria used in differentiating *Spirochaeta pallida* cultures from those of other spirochetes.

Morphology is of no value whatsoever since the forms of *S. pallida* are extremely variable in culture. Staining also of little help in definitely differentiating *S. pallida* since *S. pallida*, as the name implies, stains poorly. Culture also cannot be used since the cultivation of *S. pallida* has not yet been worked out. Albrecht states that he cannot here discuss the problem of *S. pallida* culture, on which numerous studies have been made in the past 36 years, but that he wants to mention the fact that the earlier authors who had succeeded in culturing *S. pallida* were themselves doubtful that these cultures represented true cultures of this organism. That serology with its methods for the differentiation of spirochetes, in view of the above described status of the culture question, cannot be utilized seems obvious, since serologic studies can be applied with certainty only when absolutely pure cultures are used.

The reproduction of the same disease by means of a pure culture of the same pathogenic organism in a normal being, which is the last requirement of Koch's triad, has been the goal which all of the earlier investigators have tried to attain in animal experiments in order to determine definitely that their cultures were true cultures of *S. pallida*. Therefore of all the microbiologic methods the only method of value for the identification of *S. pallida* at the present time is that of lymph node transfer and of superinfection of animals having a latent infection.

Albrecht explains the fact that syphilitic lesions have been produced with cultures by attributing the apparent virulence of the cultures to the fact that some *S. pallida* have been preserved in the culture medium but that they have not multiplied in the culture. This view is supported by the fact that the so-called *pallida* cultures lose their pathogenicity after more or less numerous transfers. He says it is possible to keep such cultures growing for many years because only the saprophytic spirochetes have retained the power of reproduction.

Albrecht and coworkers also considered proof of pathogenicity and infectiousness to be essential in identifying any culture of spirochetes submitted to them for immune-biologic studies. Albrecht here states that he investigated the spirochetal strains of Hilgermann and of E. Hoffmann, of which he had obtained comparatively early transfers, in a large series of animal experiments. He found these strains to be nonpathogenic in all of the rabbit transfers and they in no way resembled *S. pallida*. E. Hoffmann later himself recognized his strain to be a non-*pallida* strain.

With the five transfers of Hilgermann's spirochetal culture, of which only the fourth was free from bacterial contamination, experiments were carried out on 74 rabbits and 50 mice. The results showed that neither in the direct experiment nor by means of lymph node or brain transfer of rabbits and mice to normal animals, nor by means of superinfection with *pallida* strains could either a

manifest or latent syphilitic infection be produced in the animals infected with culture transfers. These results showed conclusively that the Hilgermann spirochetel cultures submitted to Albrecht contained no *S. pallidae* which could be demonstrated in the animal experiment. In answer to Hilgermann's criticism that several transfers of cultures should have been carried out on phosphorus-free medium in order to reestablish the virulence of his spirochetes, Albrecht replies that he has not even attempted this problematic method because on the basis of his experience with lymph node transfers the body of a susceptible healthy animal could be expected to have a much better regenerative effect on the spirochetes than the above procedure.

Albrecht poses two questions.

1. Has Hilgermann cultured *S. pallida*? He answers it by stating that in spite of the great significance of this question the final solution of which would be as important as the discovery of *S. pallida*, Hilgermann has furnished no evidence to support his claims. Since Hilgermann's culture method was first reported 10 years ago, no one else has even attempted to test its suitability for the growth of *S. pallida*. It was not until 1940 that Göhring reported that with the method of Hilgermann the attempted culture of *S. pallida* was unsuccessful. Albrecht states that since Hilgermann furnished no proofs for his claims, the experience in regard to the culture of *S. pallida* which has been recorded in the world literature and the lack of pathogenicity of his cultures as determined by Albrecht are sufficient basis at least to doubt that Hilgermann has cultured *S. pallida*.

2. Has Hilgermann rendered *S. pallida* nonpathogenic by means of his culture method? This question is really already answered because of the doubt that actual *S. pallidae* were present in the cultures for any length of time. Furthermore, there is no reason for not assuming that Hilgermann's cultures had the same fate as those of other investigators who used a differently prepared medium.

The treatment of syphilis with Hilgermann's vaccines—Hilgermann himself never refers to his spirochetel vaccines or *S. pallida* vaccines—consists not of *S. pallidae* which have been made nonpathogenic but at best of dead pathogenic and/saprophytic spirochetes.

In conclusion Albrecht suggests that in case Hilgermann does not give a more detailed report of his method and results and does not submit his cultures to a recognized spirochete investigator, further studies should be made with young cultures. In order to prevent an infection with saprophytic genital spirochetes, spirochete material should be obtained from rabbits with closed testicular syphiloma. A well known *pallida* strain should be used to infect these rabbits and submitted at the same time to the investigators at the Landsberger Institute (where Hilgermann is) and to others who wish to inoculate these cultures on Hilgermann's medium and to observe them. The animal experiments which would be carried out by all investigators following each positive transfer would serve to clarify the question whether *S. pallidae* become nonpathogenic and would fulfill the conditions for making isolated cultures. Albrecht states that in addition to his own institute there are undoubtedly a number of others able and willing to cooperate in solving a problem which is of the greatest significance for the knowledge and control of syphilis.

Hyperpyrexia and the specific gravity of blood. Stafford L. Osborne. *Arch. Phys. Therapy*, Chicago, 22: 407-409, July 1941.

Several investigators have explained the blood count changes in hyperpyrexia therapy as due to concentration phenomenon, and decreases in plasma volume have been observed after artificially induced fever in animals. Gibson and Koppe have demonstrated decreased blood plasma volume, as well as decreased total blood volume, after induction of fever.

In the present study a temperature of 104° F. maintained for 4 hours was in

ced in 10 arthritic patients by means of the inductotherm and the heat-insulated cabinet. Fluid containing sodium chloride was given both as to quantity and rate according to the patient's need. Once the primary object of the study was to ascertain changes in the blood density under conditions of the therapeutic regimen. It is believed to be of considerable importance that once the temperature plateau was reached, the patient's environmental temperature was usually maintained below, or at, the level of the rectal temperature.

Thirty determinations of the specific gravity of the blood and 40 determinations on the percentage change of blood solids were made. These were made before induction of fever, at the temperature plateau, 4 hours later, and finally when rectal temperature had returned to normal. No significant changes in the specific gravity of the blood were found.

Osborne says that apparently increased blood density is not the mechanism responsible for the changes occurring in the blood cell count when adequate fluids are administered during the course of treatment. Data from these experiments confirm those given by Gibson and Kopp that there is a direct relation between the gross water loss and the environmental temperature of the patient. The significant changes which occurred in the specific gravity of the blood of these patients may be explained in part as due to the lower cabinet temperatures maintained. Therefore, it is obvious that there are definite advantages in the method for hyperpyrexia which requires the lowest environmental temperature for the induction and maintenance of the desired febrile plateau.

Renal lesions resulting from sulfathiazole. D. R. Climenko and O. W. Barlow. *Lancet*, London, 1: 770-771, June 14, 1941.

It has been pointed out that while there is a rational basis for the administration of alkali during the course of therapy with sulfanilamide, no such rationale exists for the use of alkali during therapy

with sulfapyridine or sulfathiazole. In this letter to the editors, the authors state that this statement is true insofar as the production of acidosis is concerned, for neither sulfapyridine nor sulfathiazole will produce the alkali loss known to follow the administration of sulfanilamide. It fails, however, to take into account the fact that these drugs are more soluble in neutral or slightly alkaline media than in acid media.

The practical importance of the increased solubility of these compounds as the pH of the menstruum approaches neutrality or becomes alkaline is of the highest order. One of the principal toxic reactions of sulfapyridine and sulfathiazole is their tendency to form calculi in the renal tract with a resultant interference in renal function.

The urine of patients given large doses of certain sulfonamide compounds often contain masses of insoluble crystals, and many cases have been reported in which these crystals have caused serious disturbances or even death. The administration of the drugs to animals has produced the same toxic effect. The authors describe experiments with five monkeys who were given 1 gm. per kg. per day for 28 days of sulfathiazole by stomach tube, without sodium bicarbonate. A second series of five monkeys was given the same dosage of sulfathiazole plus the same amount of sodium bicarbonate (1 gm. per kg. per day). Four of the five animals in the first group died, and autopsy showed severe inflammation of the renal tract involving the renal medulla, the renal cortex, the renal pelvis, the ureters, and the bladder. In the second series no untoward effects were observed, and all animals survived 28 days of medication. In two animals of the second group, sacrificed on the 29th day, no macroscopic lesions could be found, and histologic examination revealed only slight parenchymatous degeneration.

In the opinion of the authors, the striking difference in the renal lesions in the two series can only be attributed to an increased solubility of the drug in the slightly alkaline urine resulting from the

administration of the sodium bicarbonate, which is sufficient to prevent the precipitation of the drug in the renal parenchyma and thus maintain the integrity of renal function, in spite of excessive medication.

PUBLIC HEALTH ADMINISTRATION

Ohio joins States requiring premarriage examination. Ohio State M. J., Columbus, 37: 784-788, Aug. 1941.

A large number of persons and practically every physician in Ohio will be directly affected by a measure (Senate Bill 141) passed by the 94th General Assembly, which will become a law on August 18, 1941, requiring each applicant for a marriage license to furnish a physician's statement, rendered after an appropriate medical examination, to the effect that such applicant is not infected with syphilis, or if so infected, is not in a stage of that disease which is communicable or likely to become communicable.

Section 11186, which covers the solemnization of marriages in churches which require the publication of banns, has been amended to require that, before the first publication of the banns, the clergyman or spiritual head of the church in which the banns are to be published must secure from the persons desiring to be married evidence of the fact that a statement signed by a licensed physician of Ohio has been filed with the clerk of the probate court of the county in which the woman resides. This statement must certify that, in the opinion of the physician, neither of the applicants is infected with syphilis in a form that is or is likely to become communicable. It must show that an acceptable serologic test for syphilis was performed.

No license may be granted when either of the parties is an habitual drunkard, epileptic, imbecile, or insane person, or when either of the parties is under the

influence of an intoxicating liquor narcotic drug.

A list of laboratories approved by the State department of health is given. Acceptable tests are the Eagle, Hint, Kahn, Kline, and Kolmer. The State department of health laboratories will perform the tests only when the physician certifies that the applicant is unable to pay for a serologic test in an approved laboratory.

If either or both of the applicants for a marriage license are resident of another State which has a similar law requiring serologic test and a physician's examination before marriage, the applicant must present a certificate from an officer empowered to issue marriage licenses in that State, certifying that the laws of that State have been complied with and that the applicant's physical condition is such that he could be married in that State. The physician's statement shall be accompanied by a statement from the person in charge of the laboratory making the test. This statement shall give the name of the test, the date that it was made, the name and address of the physician to whom a report was sent, and the name and address of the person whose blood was tested. The results of the test shall not be given on the statement.

More new laws to guard family health

A summary of State legislation for premarital and prenatal examination against syphilis. W. George Gould, J. Social Hyg., New York, 27: 277-279, June 1941.

Popular enthusiasm continues for premarital and prenatal examination laws as effective means of protecting home and family life from the menace of syphilis. Since 1935, when the first legislation of this type was adopted in Connecticut, 38 States have passed either premarital or prenatal examination laws, or both, setting an unusual record for law-making speed and activity.

During the past legislative year five States passed laws to encourage syphilis-free marriages. They are Iowa, Maine, Ohio, Utah, and Vermont. A total of 2

tates now require the prospective bride and groom to submit, before issuance of the marriage license, to examinations including a blood test for detection of syphilis. Seven other States have laws which require either a physician's certificate for the male only for freedom from venereal disease, or prohibit marriage of persons with venereal disease, or require personal affidavit of freedom from syphilis. Some additional bills were pending when this article was written. In other States similar legislation is already under consideration for the next legislative year.

Twenty-five States now seek to protect the health of babies by requiring that physicians include a serologic test for syphilis as a part of the examination of every pregnant woman. Six of these states (Connecticut, Nevada, Oregon, Utah, Vermont, and Wyoming) passed laws to this effect during the 1941 legislative year. In some States, legislation of this type is still pending. Similar bills are being prepared in other States for consideration in 1942.

Under this type of law physicians and midwives are required to see that blood tests are secured on pregnant women who seek prenatal care. Medical records show that if a syphilitic condition is discovered early in pregnancy and adequate treatment given, the baby has a 95-percent chance to be born free from syphilis.

Health in Iceland. Vilmundur Jónsson. Reprint from the Report on Public Health in Iceland 1938. 29 pages. Reykjavik, 1940.

Venereal Diseases Act (amended last in 1932) (p. 18).—The Venereal Diseases Act, as enforced in 1932, places emphasis on general instruction about the nature of these diseases, directions for direct prevention against infection, and facilities for the patients to obtain safe medical aid which is provided at the expense of the public, including stay in hospitals when necessary. A free clinic is maintained in Reykjavik for this purpose by a specialist who receives a permanent salary from the State. In other places

venereal cases can get free treatment from the district physicians. Iceland is a party to an international agreement (Brussels, Dec. 1, 1924), facilitating medical treatment of venereal diseases for sailors of the mercantile marine.

Venereal diseases (p. 26).—"Gonorrhea is endemic in the towns, especially in Reykjavik, although numerous cases are brought home from abroad by Icelandic seamen and other seafaring people, or the infection may be traced to foreign seamen who stay in this country. Besides this, gonorrhea occasionally occurs in villages and fishing stations, but it is only very rarely that a case is found in the rural districts. During the last few years 400-600 cases (including foreigners) have been recorded by doctors, and it seems that the disease is rather increasing. Syphilis is, on the other hand, very rare in Iceland and in by far the most numerous cases infection took place abroad, but it does, however, happen that an occasional infection is effected in the country itself. Chancre (ulcus molle) may be said to be unknown as far as the Icelanders are concerned. Freedom in love affairs and sexual licence is undoubtedly no less among the Icelanders than is the custom with other people, of which various evidences may be seen (illegitimate children about 20 percent). On the other hand prostitution hardly exists at all in Iceland."

How many people have syphilis? A brief report on prevalence of syphilis in the United States. Charles Walter Clarke, Marie di Mario and Mary S. Edwards. *J. Social Hyg.*, New York, 27: 269-276, June 1941.

The authors state that some dissension has recently arisen concerning the accuracy of estimates of the prevalence of syphilis in the United States. Many widely differing estimates have been issued, but these differences may be attributed largely to variations in the interpretations of figures. There has been confusion in employing terms commonly used in discussing the prevalence of syphilis. The error is frequently made

of attributing to the whole population a rate of prevalence based on a small and unrepresentative portion of the population. A clear statement of the criteria used to indicate the presence of syphilitic infection is sometimes lacking.

There are four important points to be considered in estimating the prevalence of syphilis: (1) The population sample should be divided into the same sex and color ratios as that of the entire population. Age and economic factors are significant in connection with syphilis. (2) All examinations included in the survey should be routinely performed. (3) A suitable period of time should be selected during which examinations included in the survey should be performed. (4) Serologic tests used as a criterion for determining the presence of syphilis involve a certain amount of error in the direction of underestimation. False negative tests greatly outnumber false positive tests.

The authors compiled reports of serologic tests on a total of more than 4 million persons. Each group study reported was then carefully reviewed from the above four points, and it was found that many of the tests were not performed according to the requirements for inclusion in this study. Only tests made during the years 1935 through 1940 were used. After elimination on the basis of time limit and on the routine nature of performing the blood tests, a total of 1,897,599 cases remained for the years 1935 through 1940.

Of the 1,897,599, 61,403 (3.24 percent) were positive. Of 458,878 males, 15,060 (3.28 percent) had positive tests. Of 613,707 females, 14,996 (2.44 percent) had positive tests. Of 694,890 white persons, 10,051 (1.45 percent) had positive tests. Of 110,823 Negroes, 16,687 (15.06 percent) had positive tests. Thus, the crude rate was 3.24 percent. The rate weighted by sex was 2.86 percent. The rate weighted by color was 3.13 percent. The authors assume, for all practical purposes, that the prevalence of syphilis in the United States was 3 per 100 population for the period 1935 to 1940.

The percentage of positive tests found among various groups was as follows: (1) 741,088 applicants for marriage licenses, 1.37 percent; (2) 282,667 expectant mothers, 1.69 percent; (3) 299,800 hospital patients, 5.58 percent; (4) 22,800 persons in various relief groups, 9.16 percent; (5) 183,718 industrial employees, 5.43 percent; (6) 37,185 domestic servants, 11.70 percent; (7) 37,647 food handlers, 4.95 percent; (8) 5,066 barbers and beauticians, 5.74 percent; (9) 4,686 blood donors, 1.71 percent; (10) 475 midwives, 5.26 percent; (11) 12,001 jail inmates, 19.75 percent; (12) 155,497 private patients, 3.06 percent; (13) 7,366 enlistees, 1.72 percent; (14) 4,287 life insurance applicants, 1.00 percent; (15) 10,100 students, 0.37 percent; (16) 93,479 miscellaneous voluntary examinations, 3.00 percent.

The rate of 3 percent is a general rate based on a Nation-wide sample, and it is not applicable to any one region. The authors conclude that it seems to be desirable to collect data of this nature systematically so that some trend may be established and so that the extent of the prevalence of syphilis may be determined for occupational, age, and color groups.

The social cankers. Otey J. Porter, *Southern Practitioner*, Nashville, 30: 7-17, Jan. 1915. (Also *J. Tennessee Medical Association*, M. A., Jan. 1915.)

This address, delivered as the President's Address at a public meeting of the Middle Tennessee Medical Association in 1914, has been reprinted and distributed in 1941 by permission of the author. Porter began his address by saying that the physician who ventures to discuss publicly the relation of venereal diseases to social welfare must forego the hope of popular approval and become an adept at dodging verbal brickbats. If he did not hope for the final triumph of knowledge over ignorance, he would not be so foolhardy as to invite the odium incident to discussing this tabooed theme. He believed, however, that the game was worth the candle.

Two principal methods of attacking venereal diseases have been tried from time to time; one is moral culture, the other legal force. Both are failures. The first ignores what is self-evident on every hand, that moral restraint operates ineffectually in the presence of passion and opportunity. The second plan has completely failed in Europe and in the parts of the United States where it has been tried. The spread of plague or cholera could not be controlled by segregating one fourth of the persons in a town and allowing the other three fourths to visit them as they desired.

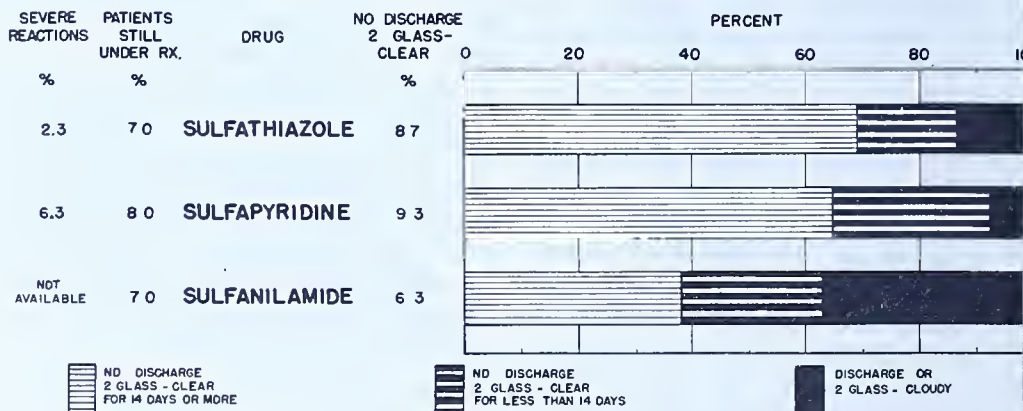
Porter says the only sensible way to cope with the menace is to look on the so-called venereal diseases in exactly the same dispassionate, scientific spirit as all other communicable diseases are viewed.

The purely material matter of preventing them must be entirely dissociated from the question of sex morality. Venereal diseases should be made reportable. The extent and consequence of them should be made as familiar to the public as they are to physicians. Adequate personal instruction should be supplied as to the means and measures that will prevent infection where the possibility of infection may exist. If progress in the way of lowering the rising tide of these diseases is ever to be made, prejudice must be laid aside and the scientific principles of prevention applied. Porter emphasized there is no inconsistency between preaching idealism with reference to sex relationship and teaching prophylaxis with reference to venereal disease.

RAPID APPRAISAL OF SULFONAMIDE DRUGS IN THE TREATMENT OF GONORRHEA IN THE MALE

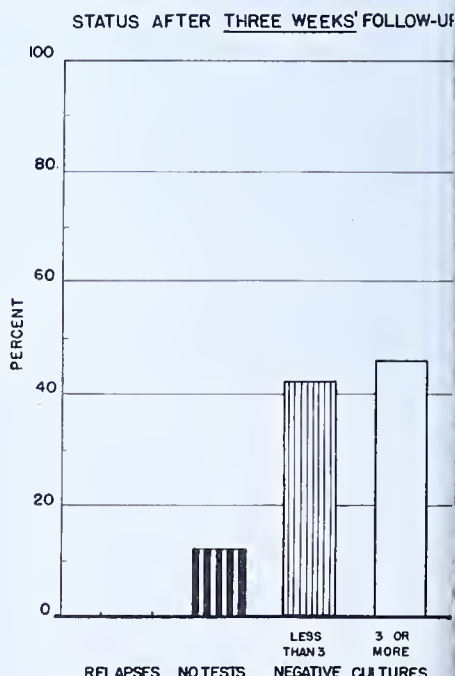
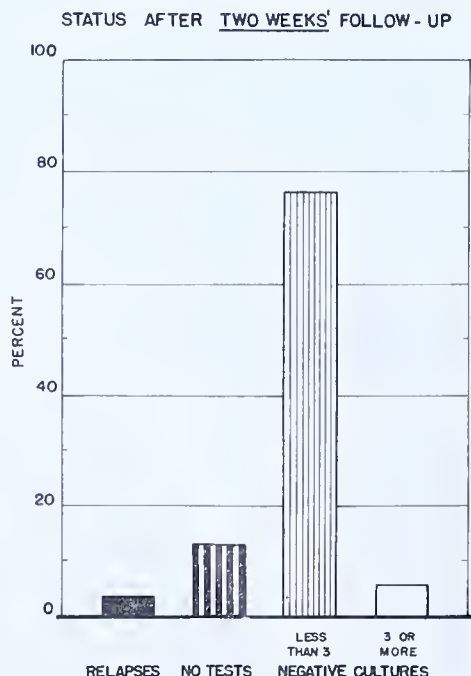
MONTHLY REPORT

DISAPPEARANCE OF SYMPTOMS BY END OF FOURTH WEEK OF OBSERVATION



SULFATHIAZOLE

LABORATORY FOLLOW-UP IN INDICATED PERIODS ON PATIENTS SHOWING NO DISCHARGE AND CLEAR 2 GLASS TEST FOR 14 DAYS



NEW DRUGS

RAPID APPRAISAL REPORTS ARE PUBLISHED EACH MONTH ONLY FOR DRUGS IN GENERAL USE. RESULTS WITH NEW DRUGS INTRODUCED FOR CLINICAL EXPERIMENTATION ARE COMMUNICATED DIRECTLY TO THE RESEARCH CLINICS AND TO THE PHARMACEUTICAL LABORATORY MANUFACTURING THE DRUG. THIS INFORMATION IS AVAILABLE TO OTHERS UPON REQUEST.

The Significance of Syphilis in Pregnancy

Preliminary Report

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SYPHILIS IN pregnancy is important because of the intimate relation which the mother bears to the fetus. It provides one of the closest and yet most completely nonsexual contacts with which the epidemiologist in this field has to deal. Here is certainly one instance in the course of syphilitic infection where the innocent bystander may be affected. Because of the innocence of the child in relation to infection with congenital syphilis, the control of syphilis in pregnancy has been regarded with the utmost sympathy and interest by physicians, health officers, and the public, alike.

It was recognized long ago that a syphilitic pregnant woman could transmit the infection to her offspring. Paracelsus, as early as 1529, apparently understood the true significance of congenital syphilis and was even aware of the fact that under some circumstances syphilitic fathers did not pass the infection on to the child. His work, however, was neglected until 1738 when Astruc became interested in the subject and rediscovered and developed Paracelsus' ideas. Shortly thereafter, John Hunter introduced some of the most amazing misconceptions in the history of clinical medicine. He not only insisted that syphilis and gonorrhea were the same disease, but he vehemently denied that syphilitic pregnant women could transmit the disease to their progeny. Because of the high respect which Hunter enjoyed, his doctrines were accepted by most of his contemporaries.

Read at the Eleventh New England Health Institute, Boston, Mass., April 3, 1941.

Fifty years later the French investigator Ricord put clinical syphilology on a sound basis by conclusively refuting the false ideas of Hunter. An interesting observation made at this time by Colles has come down to us as Colles' law: "One fact deserving our attention is this: that a child born of a mother who is without any obvious venereal symptom and which, without being exposed to any infection subsequent to the birth, shows this disease when a few weeks old; this child will infect the most healthy nurse whether she suckle or merely handle and dress it, and yet the child is never known to infect its own mother even though she suckle it while it has venereal ulcers of the lips and tongue." Colles made no attempt to interpret this phenomenon of the mother's immunity to her syphilitic infant, but it is probable that he understood its implications, namely, that the mother had syphilis. A few years later Hutchinson described the famous triad, interstitial keratitis, Hutchinsonian teeth, and deafness, and noted even before Kassowitz the decreasing virulence of the mother's syphilitic infection for the child with successive pregnancies. The modern history of syphilis begins with the discovery of the etiologic agent in 1905, the Wassermann test in 1906, and salvarsan in 1910, and continues with the development of improved serologic tests for syphilis by Kahn, Kline, Hinton and others, the introduction of bismuth and recently mapharsen, and the current investigations of intensive drip therapy. The studies by McCord (1), McKelvey

and Turner (2), Cole (3), the Cooperative Clinical Group studies (4) (5), and others have done much to elucidate the problems connected with syphilis in pregnancy.

DIAGNOSIS OF SYPHILIS IN PREGNANCY

There is evidence which suggests that the diagnosis of syphilis in pregnant women is more difficult than in nonpregnant women because of the ameliorating influence of pregnancy on the course of the disease. The use of the serologic test for the detection of syphilis in pregnancy is of the utmost importance and has received the emphasis which it deserves. The idea expressed in the literature some years ago that pregnancy may be one of the causes of a false positive test finds no justification in fact. The causes of false positive tests, such as leprosy, yaws, infectious mononucleosis, febrile conditions, might, of course be present in pregnant as well as nonpregnant women, but there is no evidence that pregnancy of itself causes false positive reactions. On the other hand, no test detects 100 percent of cases, the sensitivity of most tests varying from 70 percent to 85 percent. A certain proportion of pregnant women with undoubted infection, therefore, will not have positive reactions. In these, the diagnosis has to be based on a careful history and physical examination. One rule to which there is no exception and which is the explanation for Colles' law is that any woman who gives birth to an infected infant has syphilis herself, regardless of any serologic finding. Examination of the pregnant woman for syphilis, including a properly performed serologic test, should be done early in pregnancy, preferably before the fourth month. The Cooperative Clinical Group also advises that the serologic test be repeated toward the end of pregnancy, at about the seventh month, so that those women who acquire the disease during pregnancy will not be missed. The diagnosis of the disease in pregnancy requires as much care and interpretation as in all other cases and should not be made on the

basis of a single positive serologic test unless there is definite evidence of syphilitic infection in the history or in the physical examination. There is no reason for relaxing the criteria in the diagnosis of syphilis simply because the woman is pregnant. In a patient without other evidence of syphilis, a positive test should be repeated before the diagnosis is made and treatment is started. The interpretation of tests that vary from positive to negative to doubtful may be very difficult and should be left to the expert syphilologist. Once the diagnosis is established, every effort should be made to determine whether or not the mother has acquired or congenital syphilis, since the prognosis as to congenital syphilis in the baby can be so entirely different.

THE STATISTICS OF SYPHILIS IN PREGNANCY

There is evidence that there has been a real decline in the incidence of syphilis in pregnancy, and, therefore, in congenital syphilis during the last 20 years. In a study made by Hinton (6) of the serologic reactions of 7,755 pregnant women who were being followed in Massachusetts prenatal clinics for the 5-year period 1915-1919, 5.1 percent had positive, and 4.8 percent doubtful Wassermann reactions. In 1935 Nelson (7) repeated the study of the incidence of syphilis in pregnancy in clinic patients for the years 1930-1934. Among 17,624 pregnant women, it was found that 1.5 percent had a positive Wassermann or Hinton reaction, and 1.1 percent had doubtful reactions. There is reason to believe that the incidence is much lower in patients who go to private physicians.

The incidence of congenital syphilis in any community will vary directly with the incidence of early syphilis in the women of that community. In general the higher the number of women with early syphilis, the higher the number of babies who will be born with the disease. It is therefore encouraging to note the many evidences of the decline of early syphilis in Massachusetts. The incidence

of reported early syphilis has declined from a rate of 56 per 100,000 in 1926 to 15 per 100,000 in 1940. There are other evidences of a real decline in early syphilis in Massachusetts, into which I need not go at this time. Many other sections of the country also possess data which suggest a real decline in the number of early cases.

It is extremely difficult to estimate the exact number of babies who are affected in one way or another by syphilis in the mother. The figure of 60,000 infants born alive with syphilis each year is the estimate put forward by the Cooperative Clinical Group. This is necessarily based on very crude data, and is probably too conservative. Furthermore, it does not include those infants who die before or at the time of birth from syphilitic infection. The reported cases of congenital syphilis below the age of one year in Massachusetts since 1930 show no distinct trend until 1937, since which time there has been almost a disappearance of this type of reported syphilitic infection. In 1940, only eight cases of congenital syphilis below the age of one year were reported.

THE EFFECT OF SYPHILIS ON THE CHILD IN UTERO

Syphilis may have variable effects on the child in utero, depending upon many factors, of which the most important are the duration of infection in the mother, the amount of treatment received by the mother before pregnancy, the amount of treatment received by the mother during pregnancy, and the time during the pregnancy at which treatment is started. No one of these variable factors can be considered independently of the others, a practice which has been so common in the studies of the last 15 years. The fetus may be infected relatively early in pregnancy and be destroyed by an overwhelming infection with resulting death and miscarriage. A less severe infection may cause death of the infant late in pregnancy, or at full term. Some infants are born apparently normal, only to develop serious compli-

cations during the first few months of life to which they may succumb. Others appear normal at birth and continue to appear normal until the period from 8 to 15 years, at which time interstitial keratitis or some other late complication of congenital syphilis may develop. Finally, there are those children born with syphilis who never show any manifestation whatsoever of the disease, and who may be discovered by routine blood tests later in life. The observations of Hutchinson and Kassowitz probably provide the best explanation of the varying reaction of the fetus to the infection of the mother. The earlier the mother's stage of infection, the more extensive the spirochetemia is likely to be, and the more overwhelming the involvement of the fetus. It therefore follows that miscarriage due to syphilis can be expected to occur most commonly in those mothers whose duration of infection is relatively short; within 2 to 3 years. Stillbirths, and infants so severely infected as to fail to survive the first few months of life, also fall into this same category, i. e., they are likely to be the progeny of women who have early syphilis. Conversely, the longer a woman has the disease, the less likely she is to have a miscarriage or stillbirth, and the less likely the baby is to suffer in any way from the infection in the mother. It should be clearly understood, therefore, that in the absence of any treatment whatsoever, time has a decidedly salutary effect upon the course of syphilis in pregnancy so that succeeding pregnancies result in fewer and fewer of the more serious tragedies of congenital syphilis. That occasional exceptions occur no one can deny. Many observers have described the occurrence of acute syphilis in the offspring of mothers whose infection was of more than 10 years' duration, but these are certainly the exceptions rather than the rule.

Treatment of syphilis in the mother before and during the pregnancy is the other great factor which determines the outcome of the pregnancy. Evidence has been produced by the Cooperative Clinical Group

and other investigators that good anti-syphilitic treatment before pregnancy markedly improves the outlook for the child. It is unusual for a mother who has been adequately treated before pregnancy to have a congenitally syphilitic infant. The value of treatment during pregnancy also is so well known as to need little additional emphasis. Adequate treatment during pregnancy, started, if possible, before the fifth month, insures a normal, healthy baby in a large proportion of all cases. It is important also to remember that treatment at any time in the pregnancy, even in the eighth or ninth month, is far better than no treatment at all.

The interrelation between these two major factors upon which the health of the child depends, i. e., the duration of the infection in the mother and the treatment of the mother before and during pregnancy, is a problem which needs special emphasis and elucidation. Certain tentative conclusions, based upon a study of over 1,000 syphilitic pregnancies which is being made by the Massachusetts Department of Public Health, and which throw light on this relationship, seem to be justified. In the first place, it became clear very early in our analysis that no evaluation of the effects of treatment of the mother upon the outcome of the pregnancy could be attempted without first making allowance for and giving proper weight to the duration of the mother's infection. For example, it seems obvious that inadequate treatment in pregnancy of women who have had syphilis for over 10 years will not be followed by the same disastrous consequences as one would expect to result from inadequate treatment of infected mothers whose infection is of less than 1 or 2 years' duration. As a matter of fact, the evidence suggests that inadequate treatment in a series of women whose syphilis is of long duration may be followed by as high an incidence of normal children as adequate treatment in a series of women whose syphilis is of very short duration. There are several instances in the department's study in which more than adequate treatment was

given to women who had early syphilis during pregnancy but whose pregnancies resulted in congenitally syphilitic infants in spite of this adequate treatment. The outlook for the baby, when the mother has early syphilis, is therefore much more serious than is the case when the mother has late syphilis. This relation has been recognized by many observers. Moor (8) recently said: "It is generally agreed that when one is confronted with an early infection late in pregnancy, the chances of infection of the fetus are extremely high, and for its sake also, in addition to the need of the mother, intensive treatment is imperative." It is evident, therefore, that much more emphasis should be placed upon treatment of pregnant women whose syphilis is early, and that epidemiologists and clinicians should be much less disturbed about the effect of the disease in pregnant women whose infection is old. The tentative evidence derived from the department's study suggests that a woman whose syphilis is of more than 5 years' duration will rarely transmit her infection to the fetus. It would seem that our efforts should be directed toward providing adequate treatment for infected women before they become pregnant, as well as treatment during pregnancy, and that particular emphasis should be placed upon the provision of intensive therapy during pregnancy for those women with early untreated syphilis. On the other hand, our enthusiasm should be somewhat tempered in our management of pregnant women with late syphilis, and their treatment should be milder and less intensive since the prospect for the baby is good in any event.

The rarity of the transmission of syphilis to the third generation is probably explained by this duration-of-infection factor. The woman who is born with the disease, and who marries and bears children in most cases has been infected for more than 20 years before she becomes pregnant. This time relationship alone would be sufficient to explain the rarity with which such women transmit the disease to their offspring.

The relation between syphilis in preg-

nant women to infection of the child is clarified by a consideration of the circumstances in a blood transfusion given by an infected donor. Such a donor has much the same relation to the normal uninfected patient as the infected mother has to the normal fetus. It is a well-known fact that donors with syphilis are much more likely to transmit it to the recipient if their disease is of short duration, and that, conversely, if the donor's infection is of long duration, it is extremely unlikely that the blood will contain any spirochetes with which to infect the recipient. The fetus, and particularly the placenta to which it is attached, are in a sense experiencing a constant blood transfusion from a syphilitic donor. The passage of time, and chemical sterilization of the mother by treatment, both provide a blood transfusion which contains few or no spirochetes.

Another aspect of the communicability of syphilis which throws light upon its communicability in pregnancy is conjugal syphilis, or the spread of the disease in marriage. A man who has had the infection for more than 4 years is very unlikely to take it into marriage with him, even though he has never had any treatment previously (9). On the other hand, those individuals whose infection is less than 4 years in duration usually do transmit the disease to the marital partner.

Recent studies by Kemp (10) on the infectiousness of the secretions of the body indicate that *Spirochaeta pallida* is rarely ever found in the secretions of patients with syphilis of more than 4 years' duration.

The communicability of syphilis in pregnancy is, therefore, not so much different from its communicability in other types of sexual and nonsexual contact. Problems connected with its transmission to the fetus become less confusing if the closeness of its epidemiologic relationships to other types of host-contact is clearly appreciated. It can be seen that the reduced infectivity of maternal syphilis for the fetus, when the disease in the mother is of more than 4 or 5 years'

duration, is in accord with the communicability of syphilis in relation to conjugal infection, blood transfusion, and the infectiousness of various secretions of the body. This close correlation of communicability is exactly what one would expect unless one assumes that syphilis in pregnancy follows an entirely different epidemiologic pattern than it does in any other relationship; for this assumption there is no basis in fact.

A further consideration of some interest is the age distribution of infected pregnant women whose pregnancies have a tragic outcome. If miscarriages, stillbirths, and congenitally syphilitic infants are most frequently the result of pregnancy in those women whose syphilis is of short duration, then we can expect their incidence to be higher among the younger mothers, since it is known that almost 70 percent of early syphilis occurs before the age of 30. A recent study by Dill and coworkers (11) confirms this expectation. The age distribution of their series of syphilitic pregnant women indicated that the pregnancies which ended in tragedy occurred in the younger age groups, whereas the pregnancies which resulted in normal, healthy infants occurred in the older age groups. Although the authors of this recent study did not know the duration of infection in most of these patients, they suggested that this age distribution probably was a reflection of the close relationship between early syphilis in the mothers and infection in the fetus.

The manner in which the spirochete attacks the fetus during pregnancy is not entirely clear at the present time. The evidence suggests that infection rarely if ever occurs before the fourth month of pregnancy. It is possible that the anatomic changes which occur in the placental structure are sufficient to explain this early fetal immunity. This fortunate early immunity of the fetus provides the physician with an opportunity to start treatment before actual infection of the infant has occurred, so that finding syphilis early and treating it early in pregnancy becomes doubly important.

The treatment of the disease in pregnancy requires as much individualization as does the treatment of any other type of syphilis. It will vary, depending upon the duration of the mother's infection, the treatment received by the mother before pregnancy, the sensitivity of the patient to arsphenamine and its derivatives, the presence or absence of other medical complications of pregnancy, such as nephritis and preeclampsia, the period of the pregnancy at which treatment is begun, the outcome of previous pregnancies, and possibly other factors. It has long been an obstetric rule that pregnancy should be managed in such a way as to provide first for the health and welfare of the mother. Although pregnant syphilitic women will in most cases tolerate anti-syphilitic treatment as well as nonpregnant women, it is probable that the extra burden of pregnancy provides a more favorable background for adverse reaction to treatment. In general, pregnant women with syphilis should be divided into three treatment categories, according to their duration of infection.

Mothers with early syphilis should be considered as emergencies, and intensive treatment should be instituted. In these cases, the largest possible total dose of arsphenamine or one of its derivatives should be given during the pregnancy, and it may be desirable to give concurrent injections of bismuth. In order to obtain this maximum dosage, it may be necessary to give the drug once every 5 days rather than once a week, and in some cases in which early syphilis occurs during the pregnancy, it may be necessary to administer the treatment even more frequently. The ideal method would be one which allowed the administration of large doses of the drug in a relatively short time. No such method is yet available for use in pregnancy, but recent experimental work with intensive intravenous drip therapy of early syphilis may provide a possible solution of this problem. Pregnant women with syphilis of more than 5 years' duration fall into the second category. The prognosis for the baby in these cases is good, and treatment should be considered

as added insurance and not necessarily as the *sine qua non* of prevention. In these pregnancies, a total dose of at least 10 injections of an arsphenamine derivative is desirable, and the injections should not be given more than once a week. The large group of mothers whose duration of infection is unknown, or who may have had infectious relapse so that the total duration of infection is uncertain, and those who have had irregular, inadequate treatment before pregnancy fall into a third category midway between those cases in which treatment is of an emergency nature and those in which it is of an added insurance nature. In general, treatment should not be so intensive as in the first group, but, on the other hand, more intensive than in the second group. The prognosis for the baby is entirely different in these three distinct categories. In the first instance, the baby's opportunity to survive the pregnancy is very slight in the absence of active chemotherapy for the mother. In the second instance in which the mother's duration of infection is more than 5 years, the prognosis for the baby is excellent, and a high proportion of these babies will escape infection even though the mother receives inadequate treatment. The children of mothers who fall into the third group have an outlook which is essentially midway between the other two, and their chance of being born healthy depends to a considerable degree upon the type of treatment received by the mother during pregnancy.

As an example of what not to do in the treatment of a patient whose syphilis is of more than 5 years' duration, a recent case which came to our attention may be cited. A pregnant woman with late syphilis was admitted to the hospital and was given neoarsphenamine, 0.6 gram every 2 to 3 days, with concurrent bismuth, in a somewhat hysterical effort to protect the unborn child. Actually, the outlook for this baby was very good, and the health of the mother was seriously endangered by the institution of such intensive treatment.

The management of pregnant syphilitic

women who have had adequate treatment before pregnancy is still rather uncertain. The Cooperative Clinical Group (5) advises thorough antisyphilitic therapy during every pregnancy, irrespective of the amount of treatment received previously and irrespective of the apparent clinical status, but adds: "This is said advisedly, and with the full hope that amplification of our information in the future will allow a modification of this particularly severe rule." It is hoped that when the department's analysis of the large series of pregnant syphilitic women previously mentioned is completed, the evidence for the modification of this particularly severe rule will be forthcoming.

The status of the serologic test during pregnancy also has a direct bearing upon the outlook for the child. All studies indicate that a negative serologic reaction in the mother is supportive evidence for a favorable prognosis for the infant.

The treatment of pregnant women who have congenital syphilis is somewhat uncertain at the present time. Probably most syphilologists accept the opinion that treatment of congenital syphilitics during pregnancy is unnecessary. Others believe that a congenital syphilitic should be treated during the first pregnancy if not during subsequent ones. The possibility of binary syphilis, i. e., superimposed, acquired infection, in a congenital syphilitic, provides the answer for the point of view of others who feel that congenital syphilitics should receive treatment during every pregnancy. The inescapable fact remains, however, that third generation syphilis, i. e., syphilis transmitted to the baby by the congenitally syphilitic mother, is so rare as to be almost nonexistent. There is certainly no question that the treatment of congenitally syphilitic mothers should be mild and highly individualized if any treatment is to be given at all.

The proper management of the syphilitic pregnant woman includes the follow-up of the baby. The diagnostic procedures which must be included in the investigation of the baby are at the present time in a somewhat confused state. A large volume of evidence is now at hand

which definitely indicates that a positive cord blood does not necessarily mean syphilis, and that, furthermore, even a positive blood during the first 2 months of life may not indicate syphilis in the baby. On the other hand, a negative blood test during the first 2 to 4 weeks of life does not mean that the child may not have syphilis. Davies (12), in a recent publication, suggests 3 to 4 months as the time at which the serologic test begins to have real significance. There is some, as yet tentative, evidence (13) that quantitative serologic tests whose titer variation can be followed from week to week may indicate whether a child is going to be syphilitic or normal. However, this type of serologic investigation needs additional study and confirmation.

X-ray examination of the infant, upon which so much emphasis was formerly laid, has lately been attacked from all sides so that at the present time one wonders whether its use is attended by more false diagnoses than correct ones. Certainly, many babies have been called congenital syphilitics on the basis of questionable X-ray evidence which in many cases may have been due to the bismuth injections given to the mother during pregnancy. For example, one investigator recently gave bismuth injections to a group of normal pregnant women (14) and studied roentgenograms of the offspring. He found that in a surprisingly high proportion of these infants born of perfectly normal mothers, the roentgenograms gave evidence suggestive of syphilis. Recent evidence also suggests that the X-ray findings in rickets, scurvy, and other conditions which produce pathologic changes in the bone of the infant, may be easily mistaken for those produced by congenital syphilis. Until the status of X-ray findings in the diagnosis of congenital syphilis is clarified, it would be advisable for none but the most experienced to rely upon them.

A most important consideration which should always be taken into account in determining whether or not the child of a syphilitic mother is infected is the stage of the mother's infection, since the

probability of infection in the child is vastly increased by the presence of early syphilis in the mother. The finding of suggestive evidence of congenital syphilis in the baby is much more significant if the baby's mother has early syphilis than it is in the case of a baby whose mother has late syphilis.

The outlook for the control of congenital syphilis is encouraging in view of the rapidly declining incidence of early syphilis, improved treatment for syphilis both before and during pregnancy, and the better understood diagnostic criteria for the diagnosis of congenital syphilis. The routine blood-testing of pregnant women should also be effective in preventing congenital infection, at least in those cases where the mother presents herself early in pregnancy. Although the present war crisis will undoubtedly cause some increase in all types of syphilitic infection, there is little question that, with the diagnostic criteria and therapeutic armamentarium now available, and the more adequate and thorough treatment of early syphilis, syphilis in pregnancy will become less and less significant as time goes on.

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The Social Worker and the Nurse in Genitoinfectious Disease Control

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WITH THE realization that a disaster has occurred and the lives of many are in danger but that there is a chance of saving them if there is quick action, the common impulse is to take action—to take action quickly and personally. There is no delay in an effort to analyze one's job. Everyone simply helps wherever and however he can. As the peak of the emergency subsides and less immediate action seems indicated, orderly thought comes forward, and the desire for a plan of action emerges—a plan or program which will use to the fullest the concentrated strengths of each available person, in order that this concerted strength may be welded into a solid front of attack on the danger, and at the same time be intelligently applied to rebuilding stronger foundations.

And so it was with the sudden realization of the disaster of the diseases of syphilis and gonorrhea. The book "Shadow on the Land" by Surgeon General Thomas Parran was the alarm which aroused the citizens of America to the realization of the presence of a great disaster. Individuals and groups of individuals were shocked into a desire for action and quick action. Everyone wanted to help, and persons representing many varieties of interests came forward and began to work, each in the way which, at the moment, seemed best to him.

This sudden flood of interest seemed a little overwhelming to those who had long tried to arouse it. Leadership, however, as always, emerged from the confusion and took command. Orderly planning began. Plans were adopted which would use the strengths of the various skills represented in the groups trying to help, and use them in a program which would dovetail these

strengths towards a very solid and well built organization. Departments of welfare and departments of health, social hygiene associations, hospitals, clinics, private social agencies, privately supported health agencies, child welfare workers, public health nurses, and medical social workers all have a place in the planned programs. Women's clubs, the public schools, parent's councils, the recreational associations, the churches are part of it. Each has an important part to play, and each will contribute its strength most effectively in those programs where the staffs of the agencies are familiar with the function of their co-workers.

The causative agents of the diseases are well known. Their way of attacking is known. The scope of their war front is becoming better known daily. Through legislation for prenatal and premarital examination and for selective service, we are now learning that syphilis and gonorrhea are not diseases limited to certain social strata. They are found in all classes of society, rich and poor.

The medical profession, through its researches, is teaching improved methods of treatment. It has proven that syphilis in the newborn is preventable; that both gonorrhea and syphilis are curable if treatment is begun promptly after infection and is maintained persistently. The program now seems to be centered in the need for (1) continued education of the public through individual and collective methods; (2) the provision of sufficient treatment resources; (3) holding the patients to treatment; (4) locating and abolishing the centers which spread the disease by finding the persons infected and getting them under treatment. This program requires the concentrated efforts

of all the agents previously mentioned, each contributing from his particular field his knowledge and his skill, in close collaboration with the other fields of work.

Two of the groups of workers which are playing an important part in the planned program, and which will play an increasingly important part in the future, are the public health nurses and the medical social workers. Medical social workers and public health nurses have long been partners in the battle for individual and community health. Medical social work, which was organized in London in 1895 at St. Thomas Hospital, and in the United States in 1905 at the Massachusetts General Hospital, was welcomed to the field by the older organization of public health nursing organized in the United States at Buffalo in 1885.

The function of the public health nurse in the beginning was to give skilled nursing care to the sick poor in their homes. This was originally thought of as bedside nursing care. The medical social worker was first invited into the hospital to give social help to patients whose medical care was handicapped by social difficulties. At that date, social help was largely limited to financial assistance. The steadily growing emphasis by the medical world on positive health and preventive medicine, and the researches in social and health fields into causes of illness and distress have deepened the knowledge and broadened the scope of usefulness of both medical social workers and public health nurses.

Educational centers have been developed for the preparation of workers to give the new protective services. Education in graduate schools is now recognized as a desirable preparation for the modern public health nurse and the medical social worker. Schools have been developed throughout the United States to meet the demands for this special preparation.

Both groups of workers have learned that true help is given only through a skill and a method which will enable those who are ill or drifting towards illness to understand the meaning of the

illness to themselves and to others; to understand and to use methods for the cure of illness and the prevention of disease. Both groups realize the importance of equipping the patients with knowledge and resources which will enable them to handle their own situations.

The number of public health nurses in 1939 is given as 23,000, and this number is steadily increasing as the appreciation of their services grows, and as greater opportunities for education are made available to them. They are found in industry, in departments of education, in private visiting nurse associations, in departments of public health, in rural and in urban areas. They are working in Federal, State and county social security programs. They are working as general nurses, as consultants, and as educators.

Medical social workers are employed in approximately 1,000 hospitals and clinics in departments of health, departments of welfare, child guidance centers, in the Federal, State and county social security programs, and in the Children's Bureau. They are working in both rural and urban areas. They are working in all services of the hospital. They are drawn in as specialists in the program for prevention of blindness, in the cancer control program, in the tuberculosis program, as well as in the program for control of the genitoinfectious diseases.

As clinic and hospital workers, they, as all other members of the hospital personnel—work with individual patients. Their interest is focused on the understanding of the patient as a social being and their services are directed toward helping the patient with social problems which may be influencing his health and handicapping him in his ability to follow treatment advice. They are performing a public health function by enabling patients to continue under treatment, and by tracing and educating in treatment needs and resources those who may be infected with a communicable disease such as syphilis, tuberculosis, or gonorrhea. They are helping to prevent public dependency by rendering social service

the patients with diseases such as interstitial keratitis, glaucoma, cancer, rickets, early heart disease so that these patients may understand and follow treatment advice. A report entitled "Medical Social Work in Tax Supported Health and Welfare Services," published by the American Public Welfare Association in November 1940, classifies the activities in which the medical social workers in public agencies are engaged at present as follows:

- Administrative and supervisory
- Consultative and guidance
- Case work
- Education
- Community relationship
- Program development
- Research

There is much stimulating discussion of the subjects "specialist" and "generalist." Both appear to be of value and, therefore, there is a place for both. There are those who should be classed as specialists among public health nurses and among medical social workers. As I understand the term, a specialist is a person who, through study and practice, has acquired deeper knowledge and a greater skill in some one phase of work than the general worker. To make this specialized knowledge truly productive, it must be shared. This is especially true in work with patients who have syphilis or gonorrhea. The importance of case-finding and the necessity for case-holding require that knowledge regarding the diseases be widespread; that correct diagnostic methods be understood and practiced by the general practitioner as well as by the specialist; that the meaning of the diseases and their treatment possibilities be understood by the many thousands of public health nurses and medical social workers throughout the land; that proven methods of promoting the understanding and therefore the cooperation of the patients who have the diseases or who are exposed to them be taught to those in strategic positions as health and social workers. A specialist doesn't remain a specialist unless he continues to acquire new and deeper knowledge and is given an

opportunity to continue to learn in order that he may share his knowledge. Therefore, I believe that we need both the specialist and the general worker in the fields of public health nursing and medical social work. We need special knowledge which is acquired through intensive study in a special phase of work and is added to a sound foundation of education for general work.

A demonstration of such specialization and such sharing is made at the Institute for Control of Syphilis of the University of Pennsylvania under the direction of Dr. John H. Stokes. Public health nurses, public health officials, Army and Navy doctors, private physicians, and medical social workers from all sections of the United States are studying and working together, pooling their experience and knowledge, and together working out methods and ways of increasing their usefulness as consultants and educators to the general workers who are in daily touch with literally millions of our citizens in private offices, in clinics, in industry, in schools, in social agencies, and in the armed forces.

The legislation covering premarital, prenatal, and selective service medical examinations is placing an increased opportunity and responsibility on the private physician and a person less frequently discussed—the private duty nurse. The rich as well as the poor get married and have babies. The Selective Service Act is not limited to any economic stratum of society. Startling figures are now available of the discovery of untreated disease among those who have never been, and probably never will become, clinic patients.

Dr. Parran, in his address at the annual meeting of the American Social Hygiene Association in February 1940, gave figures to show that in all fronts the movement for the control of genitoinfectious diseases "is forward and the trend up." To quote him, "We are met here in observance of National Social Hygiene Day to measure accomplishments, to report progress, to roll stones from the path of our joint efforts against venereal dis-

eases, and to chart a clear course for the year ahead."

We are nearer to a true picture of the prevalence of the genitoinfectious diseases today than ever before. We are better acquainted with the many agencies which are helping in the campaign and their activities than before. We know that human capacity is limited, and that we must each be on guard lest our enthusiasms carry us beyond our capacity to understand and to perform, and our own activities become diluted beyond the point of effectiveness. We must consider where, in all the obvious need for service, we shall place the emphasis.

We know that the peak incidence of syphilis falls between the ages of 20 and 28, and that more than one-fifth of the new cases which occur each 12 months are in adolescents between the ages of 11 and 20 years. Dr. Parran has said that "statistical studies reveal that there are at least three persons exposed to infection for every one who comes for treatment, and it is usually true that two of the three need treatment, but have not been aware that they needed it, or how and where to get it."

The National Defense Program, with its mobilization of men in the armed forces and in industry intensifies some of our well-known social problems such as housing, sanitation, and the migrant; revives some of the old problems such as commercialized prostitution; and creates new problems which must be met through both mass and individual effort.

Abnormal living, war hysteria, greed and selfishness are increasing the spread of the genitoinfectious diseases in the civilian population. Military authorities are enforcing treatment of the man with a communicable disease. The community must protect itself from the spread of the disease.

We are told that in the population as a whole, more than one million prospective mothers have syphilis, and that as a result, 25,000 babies are born dead yearly and an additional 60,000 annually are born alive but are the victims of this disease. We know that if syphilis is dis-

covered before the fifth month of pregnancy and adequate treatment is provided the infant as a rule will be free from syphilis. Do not these statistics point to the places for emphasis?

Measures and methods for case-finding and case-holding have been much discussed. It has been proven that follow-up of the lapsed patient is more expensive and yields fewer returns than the approach through clinic interviews. The first interview with the patient in the clinic or private office continues to be the most strategic opportunity for case holding and contact-tracing. Very skillful interviewing is indicated in all places where syphilis is discovered and treated. This is true in civilian medical service and in the service to the man examined under the Selective Service Act, as well as with the man under treatment by military authorities.

We are taught the relationship that syphilis bears to cardiac disease, deafness, blindness, and mental diseases, and that gonorrhea bears to pelvic inflammatory disease and ophthalmia neonatorum. Syphilis and gonorrhea are discovered in the examination of patients in many of the specialized departments of a polyclinic. It is as necessary for the social workers in the cardiac department, the department of ophthalmology, the prenatal clinic, and elsewhere to help the patient understand his need for treatment and to help him get it, as it is for the worker in the syphilis clinic to help him to treatment when he reaches the genitoinfectious disease clinic. There is danger of many lost patients between the services of an out-patient department. The syphilis clinic treats patients of all age groups. It is of special importance both for opportunity for cure and for prevention of the spread of disease, that the young age group should be given careful attention. The figures on prenatal syphilis place responsibility without question on a method of selection which will provide very skillful social service to the patients of the obstetrical service. As 10 percent of all babies born in the United States last year were born in hospital

the opportunity for service is great and should have a lasting influence.

The discovery of the disease creates both personal and environmental problems for the patient. An intelligent and sympathetic understanding of these problems is the first step in holding the patient to treatment and in discovering contacts. But understanding is not sufficient! The patient should have help in meeting the environmental factors which are complicating his situation, as well as the more subtle help required to enable him to face his emotional problems. The clinic worker should be qualified to render the social help which is indicated. In some cases she can give direct service to the patient. In others she organizes help through cooperating agencies. This implies an ability to diagnose the patient's needs, and an understanding of the function of the community agencies, as well as an effective working relationship with them.

Direct service by clinic personnel is effective in contact-tracing and case-holding with a large percentage of enrolled patients. Other measures, however, are also of great value and reinforce the clinic services.

The clinic worker should be keenly alive to opportunities for aid which she has through the nurses and social case workers who may know certain of the patients and who have good relationships with them. Interchange of information and services between the clinic worker and the community worker is essential. Duplication of efforts may mean confusion; whereas, dovetailing of energies means strength.

The general nurse has an unequalled opportunity, superior to that of any other worker, to be of service to the pregnant patient in her home. She is the one to whom a pregnant woman turns for advice and guidance. She is the one who can answer questions, can encourage family examinations, and who can make a treatment plan possible for the patient. The school nurse, or the general nurse who visits the home of the child barred from school because of syphilis or gonorrhea

has a very great opportunity to teach the meaning of the disease and to make treatment possible. She is the one who can be most effective in stimulating and encouraging the continuance of treatment, and who can help trace the sources of infection. Industries are becoming more aware of their need for adequate medical services for their employees, and are providing them either through their own departments, or through cooperation with clinics and hospitals. The industrial nurse is becoming more prominent and more important in this health program of industry. She has an opportunity to be of special help in educating the patient who has a genitoinfectious disease in the meaning of the disease to him and to others, and helping him to make treatment plans.

The public has been aroused to the dangers of the genitoinfectious diseases, methods of curing them, and ways of preventing them. The prevalence of the diseases is pretty well known. The various agents required for a well rounded genitoinfectious disease control program are known. Sweeping methods for case-finding have been adopted. Enforcement measures for case-finding and enforced treatment have been provided through legislation.

But with it all, the most important agent in the whole program is the individual patient—the known case of syphilis. He is the key agent. Without his active participation, the work of all other agents is of but temporary value. It is through the long, slow process of hour-by-hour, day-by-day examination and work with the individual patient that the disease will be controlled. Expert service to the individual patient is essential, and this service includes medical, laboratory, social service, and nursing. The most strategic time for enlisting the patient's help is at the time the diagnosis is made and the treatment plan explained to him. The first interview requires knowledge and skill in understanding human behavior and the art of helping. There is no standardized formula for the interview, for people themselves are not

standardized. There can be no fixed rule to follow.

The patient has a serious illness which is not understood either by himself or by society. Ignorance leads to fright—expressed and unexpressed. We all react differently to that which we fear. Some run away; some fight back with a defiant recklessness; some meekly surrender; some courageously face the fears and find the cause—each in accordance with his own pattern of behavior. The individual patient is merely a human being—a human being with desires and hopes and longings as have all human beings—different from his fellows only as each human being differs from the other. To enlist the active cooperation of the patient is to understand him; to appreciate the problems which the disease brings to him and to others through him; and to arm him with the knowledge which he needs in order that he may participate as an agent in contact-tracing and case-holding. The satisfied patient is an able recruiting agent.

Doctor C. C. Pierce has stated that “finding cases and holding these cases until they are rendered noninfectious, and until they have been given adequate treatment is the heart, the core, the main-spring of the entire venereal disease control program.”

The genitoinfectious disease control program requires services and skills of many varieties. The medical social workers and the public health nurses are important agents, both because of the strategic position which they occupy, and because of their education and experience which qualifies them to understand and to influence attitudes and behavior of the individual patient who is ill. The problems involved are many-sided, and they need a many-sided attack which is harmoniously planned.

SUMMARY

I have tried to show that order is coming out of chaos.

That the many interests are now recognized as having a necessary place in the planned program for the eradication of syphilis and gonorrhea.

That sweeping measures are bringing to the surface the previously undiscovered cases of genitoinfectious disease.

That the emotional accompaniment of mobilization of troops, and the free flow of money in industry are intensifying the problems of control of syphilis and gonorrhea.

That the volume of work indicates the advisability of the selection of certain groups of patients for intensive supervision.

That infected individuals still need to know what the disease means to them and to their family and friends, what treatment is required, and how to get it.

That in the planned program, the medical social worker and the public health nurse, both special and general, have responsible parts to play, and that the contribution of each is dependent upon an appreciation of the knowledge and skills each is prepared to contribute, and upon a close working relationship.

That intelligent treatment, medical and social, in the *first* contact with the patient is the most important contact in the follow-up and contact-tracing program.

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DIAGNOSIS

False positive serologic reactions for syphilis due to smallpox vaccinations (vaccinia). Francis W. Lynch, Ruth E. Boynton and Anne C. Kimball. J. A. M. A., Chicago, 117: 591-595, Aug. 23, 1941.

With the increased number of tests performed as a routine on apparently nonsyphilitic persons there has come a better realization of the number of causes of false positive reactions. Those diseases causing strongly positive reactions are of particular clinical interest because they are capable of leading to incorrect diagnosis. Vaccinia had not been generally recognized as a cause of positive serologic reactions until Moore and his coworkers recently mentioned its possibility. The authors became interested in the problem after observation of a case in which reports were received of Kolmer 3 plus and Kline 4 plus on blood taken from a student who had severe primary vaccinia. Tests performed by two different laboratories subsequently were all negative 4 months later.

Students entering the University of Minnesota have submitted to routine physical examination. In a group of students examined in 1939, the incidence of syphilis was 0.17 percent and the false positive or doubtful cases 0.8 percent.

Among 267 persons in whom primary vaccinia later developed, all specimens taken at the time of inoculation were reported negative to the Kolmer, Wassermann, Hinton, and Mazzini tests. One gave a positive reaction, and 3 gave doubtful reactions to the Kline diagnostic test. Of the 263 who gave no false positive reactions before vaccination, 16 percent reacted to one or more of the subsequent tests, 9 percent to more than one standard test. When reactions to all four tests (Kolmer, Kline, Hinton, and Mazzini) are considered, a total of 80 positive and doubtful reactions were obtained. In the majority of instances, the strongest reaction was doubtful or weakly positive.

There was considerable difference in the incidence of the false positive reactions among the various tests. The Kolmer test was the most specific. In several cases strong reactions were given by most of the technics used; such reports might have presented difficulties to the clinician had the specimen been collected as part of a routine physical examination.

When the first specimen was submitted from 15 to 21 days after vaccination, positive reactions were more common with the Hinton, Mazzini, and Eagle tests. On the specimens submitted from 22 to 28 days after inoculation, the Kolmer, Kahn, and Kline tests were more likely to give a positive reaction. The reactions remained positive for as long as 2 months in many of the persons tested; in a few persons they were still positive after 4 months. One (Kline, 1 plus) was still present at 164 days. Many of the persons in this series were tested only once after vaccination, and the incidence of false positives would probably have been quite different if specimens had been collected more frequently during the period of 2 to 6 weeks after vaccination.

In the discussion Senear said that in vaccinia there is a condition which offers great possibilities for study of biologic false positive reactions. Kline emphasizes the newer technical knowledge which can be applied to prevent or minimize the number of false reactions. Rein called

attention to the false positives which may be found in connection with acute upper respiratory infections, varicella, scarlet fever, and measles. Schoch suggested the possible value of applying quantitative studies when dealing with questionable serums.

Bilateral abducens palsy following lumbar puncture. Bernhard Dattner and Evan W. Thomas. New York State J. Med., New York, 41: 1660-1662, Aug. 15, 1941.

Bilateral involvement of cranial nerves is rare, and so far as the authors know, not a single case of bilateral abducens palsy following a simple diagnostic spinal puncture has been reported. For this reason the following case is of unusual interest.

A 36-year-old white man was admitted to Bellevue Hospital on January 22, 1940. He gave a history of having had a penile sore in 1922 for which he was not treated. From 1929 to 1938 he received irregular antisiphilitic treatment, including 88 bismuth and 38 arsphenamine injections. For six months prior to entering the hospital he received irregular treatment with mercury. His blood Wassermann reaction was always strongly positive.

The first spinal puncture was performed in July 1937. At that time the patient had severe headaches and was bedridden for 4 days, yet his physical examination revealed no neurologic abnormalities. His spinal fluid Wassermann reaction was 1 plus; Pandy, 1 plus; colloidal gold test, negative. A second lumbar puncture was done at a New York City Board of Health clinic on January 9, 1940. He became nauseated and had a severe headache 10 hours later. Though he remained in bed, he began to vomit on the third day. He had no fever or bladder disturbances. His spinal fluid Wassermann reaction was 2 plus; Pandy, 1 plus; colloidal gold test, negative.

One week following the spinal puncture the patient noticed double vision and complained of dizziness, although his headache was less severe. The next day he returned to the clinic because of his

diplopia. There the bilateral abducens palsy was diagnosed, and he was referred to the hospital. A physical examination revealed no abnormal neurologic findings except the bilateral sixth nerve paralysis. Following a cisternal puncture on January 23 his headache disappeared, and his only complaint was diplopia. By April 4 he had completely recovered.

The authors say that this case cannot be explained on the basis that syphilis can cause extraocular palsies because, besides the patient's temporary palsy, there were no neurologic signs of meningovascular syphilis, and the spinal fluid showed no other evidence of activity than a moderately positive Wassermann reaction. Furthermore, there was a spontaneous recovery, as has been reported in most cases following spinal punctures.

The theories of meningeal irritation and spinal fluid leakage are discussed in connection with reactions following spinal punctures. The authors do not consider these theories in themselves satisfactory explanations. A meningismus alone cannot explain why the headaches are less severe when the patient is in a horizontal position, why headaches do not follow cisternal puncture, or why the severity of headaches seems to be influenced by the amount of spinal fluid withdrawn. Even though leakage occurs, to explain the headaches it must be assumed that large amounts of spinal fluid are lost. There is no proof that this occurs or that leakage lasts long enough to account for the incubation period.

Two other explanations of the temporary palsy in this case are (1) a latent virus infection activated by the trauma of spinal puncture and (2) a possible hemorrhage in the nuclei of both nerves. The first is pure speculation, however, and the second seems most improbable in the absence of any damage to closely adjacent structures.

The authors conclude that the best explanation of the bilateral abducens palsy in this case is, therefore, that of a bilateral nerve trunk injury due to changes following lumbar puncture. They account for the interval of 7 days

between the spinal puncture and the onset of paralysis by an increased pressure on both nerves. From their knowledge of lumbar punctures in general, they consider this a reasonable deduction to make.

Lymphogranuloma venereum. Observations in one hundred and eighty-seven cases at Bellevue Hospital. Maurice J. Costello and Julius A. Cohen. *Arch. Dermat. & Syph.*, Chicago, 44: 391-397, Sept. 1941.

The recognition of venereal lymphogranuloma as an entity and the new and improved diagnostic procedures have resulted in an apparent increase in the number of cases of this disease. There were 187 patients treated at Bellevue Hospital from 1935 to 1939. Involvement of the inguinal lymphatic glands was 20 times more frequent in men than in women, and twice as many patients were hospitalized in 1938 as in 1935. The anorectal type occurred $1\frac{1}{2}$ times more frequently in women, and the number of patients with this type in 1938 was three times the number recorded for 1935. The primary lesion, occurring in the form of a herpetic vesicle, as an evanescent superficial papule or ulceration, or as a nonspecific urethritis, is seen more frequently than is generally recognized. Serious debilitating late complications could be diminished if the diagnoses of ulcer of the penis "cause unknown," nonspecific urethritis, and herpes progeneralis were made with the thought that any one of them might be the initial lesion of this disease.

The authors have found that mouse-brain antigen is as reliable as human antigen in the performance of the intradermal Frei test. A control test with normal mouse brain is essential. The reaction to an intradermal Frei test usually becomes positive about 2 to 6 weeks after the appearance of the initial lesion. The intravenous test is a specific check on the intradermal, and the reaction may be obtained before that of the intradermal can be demonstrated.

Differentiation from chancroid is sometimes difficult. Mixed infections, caused

by syphilis or chancroid, occurred in about 3 percent of the cases in this series. A reliable history, in addition to the clinical and laboratory findings, is necessary for accurate diagnosis. Extragenital lesions involving the mouth have been reported.

Sulfanilamide by mouth and Frei antigen intravenously, combined or separately, appear to be the most efficacious means of controlling this disease and of helping to prevent anorectal involvement. Further studies of the therapeutic effects of these agents are indicated. Early routine proctoscopic examinations should be performed on all patients suffering from this disease, as proctitis may be an early manifestation of the disease in both sexes.

TREATMENT

The treatment of gonorrheal urethritis in the male with sulfadiazine. An analysis of fifty-seven cases. Leroy W. LaTowsky, Richard B. Baker, Frank Knight and Charles A. W. Uhle. *J. Urol.*, Baltimore, 46: 89-94, July 1941.

A study of sulfadiazine in the treatment of gonorrheal urethritis in the male is presented. A total of 57 patients were studied, of whom 53 were Negroes. A total of 26 of these patients had had some type of therapy, 10 patients having purchased sulfanilamide from druggists. There were 55 patients who were followed to the completion of the study, and 51 (93 percent) were cured on an average of 8 days of treatment, with an average of 17.5 gm. of the drug. All cases received the drug in divided doses, usually 2 to 4 times a day. Of those cured, the majority received 2 gm. daily for 4, 5, or 8 days. The only symptom of toxicity was headache, and this occurred in only 5 cases (8.8 percent). The average time elapsing before the cultures first became negative for gonococci was 13 days. The criteria of cure in this study were strict

and included, as the final test, two or more negative smears and cultures of the prostatic fluid.

Four cases were failures. Two of these patients had syphilis and were receiving mapharsen (0.06 gm. per week) at the same time they were receiving sulfadiazine. This brings up the question as to whether or not mapharsen has an inhibiting effect on the action of sulfadiazine. Another case that was a failure had previously been a therapeutic failure with sulfanilamide and also with sulfathiazole. The other treatment failure failed to cooperate.

With the administration of the drug in these dosages, the blood level of free sulfadiazine ranged from 1.5 to 10.4 mg. per 100 cc. of blood and the total sulfadiazine from 2.1 to 11.5 mg. per 100 cc. of blood. There were no significant changes in the erythrocyte, the leukocyte, or the differential counts in 17 cases which were studied.

The management of gonorrhea. VI.

The sulfonamides. Neisserian Medical Society of Massachusetts. New England J. Med., Boston, 225: 228-229, Aug. 7, 1941.

The first papers in this series on the management of gonorrhea were published by the Neisserian Medical Society of Massachusetts in this journal in 1934, the fifth appearing in 1937.

It is the Society's opinion that sulfanilamide should not be used in the treatment of gonococcal infections. Early reports of its high efficiency were commonly in error because of failure to evaluate cure by cultural methods. Innumerable asymptomatic carriers were produced. Sulfapyridine cures a much higher proportion of cases, but it causes more serious reactions than sulfanilamide. Since sulfathiazole is equally effective and causes few immediate reactions, it should be the drug of choice.

In treatment, the following dose of sulfathiazole is effective: 2 gm. daily for 10 days—4 doses daily of 0.5 gm. every 4 hours. The dose for children is 30 mg. per pound of body weight but the total

daily dose should not exceed 2 gm. The fluid intake should not be restricted. In men, if there has been no clinical improvement by the fifth day, the drug should be discontinued. Since the clinical picture in women is often confused it is the rule to give the full course and to depend on bacteriologic study for proof of response.

Infections that do not respond to one course of sulfathiazole may often be cured by a second course, similar to the first, following a rest period of a week or 10 days. More than 2 consecutive courses of the drug are of questionable value. In case of drug failure, local treatment and possibly fever therapy may be indicated.

The patient should be kept under observation during treatment. If there is persistent vomiting, rash or other severe reactions, the drug should be discontinued. Moderate nausea is not ordinarily a cause for stopping the drug. Concentration of the drug in the blood seems to have no relation to the clinical or bacteriologic result.

When treatment has been concluded, the patient should be directed to abstain from unprotected sexual contacts for at least 3 months. Cultures of prostatic secretion and urine sediments in men and of exudates from the cervix and the paraurethral (Skene's) glands in women should be made from 4 to 6 times during this period. Smears should be examined, but negative smears should not be relied on as evidence of cure.

Treatment of infections in women should be started immediately if the clinical history points to gonococcal infection. Prompt treatment usually prevents extension of the infection into the pelvic cavity, or controls it if it has already occurred. Smears and cultures should be made at the first visit.

Since sulfathiazole seems to cure a high proportion of gonococcal infections in both sexes, the prompt use of this drug should result in an early "chemical quarantine" of many of the infections. It should now be possible to cure gonorrhea much faster than it can spread.

Gonorrheal ophthalmia and gonorrheal ophthalmia neonatorum. An evaluation of the treatment. Everett Barclay Muir. *Am. J. Ophth.*, St. Louis, 24: 879-894, Aug. 1941.

The data on which this thesis is based were taken from the case records of the Cincinnati General Hospital and the Children's Hospital of Cincinnati covering from 1923 through the first half of 1939. A total of 115 cases of gonorrheal ophthalmia and 126 cases of gonorrheal ophthalmia neonatorum were reviewed. There were included also 293 cases of gonorrheal ophthalmia neonatorum and 307 of gonorrheal ophthalmia taken from hospitals in other cities.

All cases of these diseases should be isolated, and efficient nursing is essential. Buller's shield, while still used on adults in most hospitals, has been discarded in some in favor of posture alone. Irrigation of the conjunctival sac is considered to be indispensable by all clinicians, boric acid solution being used in 9 out of 12 hospitals in other cities. In the Cincinnati cases intermittent iced compresses were found to be of benefit, the use of continuous iced compresses increasing the frequency of corneal ulcers. Corneal ulcers occurred much less frequently in gonorrheal ophthalmia when silver nitrate 0.5 to 2 percent solution was instilled into the conjunctival sac than when it was painted on the palpebral conjunctiva. Silver protein solutions and other antiseptic solutions were found of no value apart from their use as irrigating fluids.

The cornea should be inspected daily. Diligence and skill on the part of the doctor will save many eyes. When chemical and thermal cauterants appear unable to check corneal ulcer, repeated paracenteses or a conjunctivoplasty should be done. The general health of the patient must be maintained.

Freshly boiled, whole cow's milk, injected intramuscularly, was found to be of more value in gonorrheal ophthalmia neonatorum than in gonorrheal ophthalmia. It was the foreign protein most favored by ophthalmologists for use in this disease. Gonococcal vaccine had been

tried by a number of clinicians without success.

In the Cincinnati series sulfanilamide was used in 6 cases of gonorrheal ophthalmia and in 2 cases of gonorrheal ophthalmia neonatorum. The results were not spectacular. Seven of the 12 hospitals in other cities reported they were using sulfanilamide in the treatment of both diseases, together with local measures, and all considered it an important advance in treatment. Artificial hyperpyrexia was found of value in the treatment of severe and resistant cases of gonorrheal ophthalmia. The youngest patient thus treated in the Cincinnati group was 1½ years of age. No fatalities occurred.

Negro and white infants seemed about equally susceptible to corneal damage. Negro adults were less susceptible than white adults, although both were more susceptible to corneal ulcers than were the infants of their respective races.

Of the 115 Cincinnati cases of gonorrheal ophthalmia, corneal ulcers developed in 48.8 percent, visual impairment resulted in one or both eyes in 26.08 percent, and perforation of the cornea occurred in 16.5 percent. Of the 126 cases of gonorrheal ophthalmia neonatorum, corneal ulcer occurred in 17.4 percent, great visual impairment in 9.5 percent, and total loss of vision in both eyes in 3.17 percent. In the cases studied from other cities impaired vision occurred in 29.6 percent of the cases of gonorrheal ophthalmia and in 11.2 percent of the cases of gonorrheal ophthalmia neonatorum.

Gonorrheal ophthalmia. Treatment with a sulfanilamide derivative and injections of milk. Otis S. Lee, Jr. and Francis K. Lum. *Arch. Ophth.*, Chicago, 26: 268-275, Aug. 1941.

Seventeen children (4 to 9 years of age) with epidemic gonorrheal ophthalmia from a children's receiving home in Shanghai, China, were hospitalized and divided into three groups for a study which is reported here.

Five patients (group 1) were given four

injections of milk intragluteally. The ocular infection improved much under this treatment but still persisted after 1 week's observation. Sulfanilyldimethylsulfanilamide was then given orally with another injection of milk to shorten the period of study. After 1 to 2 days of this treatment all of the patients were cured. No complications occurred.

Five patients (group 2) were given sulfanilyldimethylsulfanilamide orally, and three of them had the first of three consecutive negative smears for the gonococcus in 4 to 5 days. Two children with corneal involvement before treatment continued to show discharge and positive smears for the gonococcus during the treatment with the drug alone. They required a second course of treatment, consisting of injections of milk together with oral administration of the sulfonamide, to cure the infection after 5 and 6 days respectively of the latter treatment. In one of these two patients a corneal ulcer developed which perforated during treatment with the drug alone.

Seven children (group 3) were given a combination treatment with sulfanilyldimethylsulfanilamide orally and milk intragluteally. Five of them had the first of three consecutive negative smears for the gonococcus on the fifth day, 1 on the sixth day, and the seventh child (who had involvement of the cornea) on the tenth day. The eye of the seventh child was clinically cured on the sixth day, however. No complications occurred during treatment.

It was shown that a combination treatment consisting of oral administration of sulfanilyldimethylsulfanilamide and injections of milk is superior to injections of milk alone in the more rapid rate of cure and also superior to administration of the drug alone in the prevention and healing of corneal complications. Under such combined therapy, 5 to 7 days of chemotherapy with two injections of milk are probably sufficient to cure uncomplicated gonorrheal ophthalmia in the acute and subacute stages without danger of relapse. Patients with corneal complications will require four injections of milk

and possibly up to 10 or 12 days of chemotherapy.

Estrogen in gonococcic vulvovaginitis in girls. A. V. Ferrari. *Gior. ital. dermat. e sif.*, Milan, 82: 142, Feb. 1941. Abs. in *J. A. M. A.*, Chicago 117: 569, Aug. 16, 1941.

Ferrari has observed 147 patients with gonococcic vulvovaginitis, ranging from 3 to 10 years of age. One group consisted of 24 patients who presented no urethral or cervical infection. They were given estrogen as the sole treatment in dose of 10,000 international units at 5-day intervals until 10 to 20 injections had been given. The second and third groups consisted of patients with and without urethral and cervical complications. The 4 patients in the second group were treated by irrigations of the external genitalia and vagina with a weak solution of potassium permanganate or with vaginal and urethral irrigations with a 2-per cent solution of strong protein silver or silver nitrate, after which a glycerin suppository containing 2 per cent of strong protein silver was inserted into the vagina. This treatment was administered twice daily until the infection was controlled and once daily for a month thereafter. The 75 patients in the third group received estrogen in the same amount as those in the first group and local treatment as given to the second group.

Gonococci disappeared from the secretions within 30 days in 18 of the first group, in 60 of the third group, and in 40 days in 34 of the second group. Recurrence took place within 6 months in 10 of 18 patients in the first group, in 29 of 60 in the third group and in 15 of 34 of the second group. Cure has been permanent up to the present (4 years after discontinuation of treatment) in 8 of the first group, in 31 of the third, and in 13 of the second.

The general health of a large number of the first and third groups improved and long standing eczema was controlled. One girl, aged 10 years, began to menstruate as the result of the treatment.

Ferrari concludes that estrogen treat-

ment is indicated only in exceptional cases of gonorrheal vulvovaginitis recently acquired and in cases without urethral and cervical involvement which are not controlled by the usual treatment.

Azotemia, acidosis, anemia and leukocytosis following sulfanilamide therapy.

George L. Wolcott. *Internat. Clinics*, Philadelphia, vol. 2, New Series 4: 47-56, June 1941.

Toxic manifestations from sulfanilamide appear to occur on a basis of sensitivity and idiosyncrasy. The cerebral symptoms, the "acidosis," and the cyanosis appear to be direct toxic effects of the drug, while the acute hemolytic anemia and the agranulocytosis must at present be regarded as idiosyncrasies. The most serious toxic reactions involve the blood cells. Acetylsulfanilamide is more toxic than sulfanilamide. The acetyl derivative is present in comparatively low concentrations in the blood but, should an occasional individual acetylate more of the drug than average, toxic symptoms might result.

Wolcott reports an unusual case of severe, prolonged azotemia secondary to an acute hemolytic anemia following sulfanilamide therapy. The patient also exhibited severe leukocytosis and a marked depression of the plasma carbon dioxide combining power. From a study of this case, augmented by a review of the literature, Wolcott concludes that sulfanilamide may cause: (1) In hypersensitive individuals an acute hemolytic anemia, characterized by rapid fall in erythrocytes and hemoglobin, hyperbilirubinemia with jaundice, reticulocytosis and marked leukocytosis. (2) Renal insufficiency characterized by oliguria and azotemia, secondary to the intravascular hemolysis, because of (a) deposition of acid hematin in the renal tubules in acid, concentrated urine; (b) crystallization of free or conjugated sulfanilamide within the tubules; or (c) "renal anaphylaxis." (3) Disturbance of the acid-base balance of the blood (a) with the production of a carbon di-

oxide deficit type of alkalosis from primary hyperventilation, or (b) with the production of acidosis from failure of the renal tubules to reabsorb base and bicarbonate. Although these idiosyncratic reactions to sulfanilamide are usually characterized by recovery, fatalities may occur.

The case reported was that of a Negro circus worker, admitted to Bellevue Hospital because of sore throat, malaise, and cough. Two years previously he had had a penile chancre for which subsequent treatment was inadequate. The white blood count on admission was 20,000, urine normal, NPN was 33 mg. per 100 cc., blood Wassermann reaction strongly positive. Sulfanilamide was begun on the second and was stopped empirically on the fifth day after a total of 19.2 grams had been administered. On the eighth day the patient was acutely ill. On the ninth day the white blood count was up to 55,600, the red blood count was 2.08 million with 46 percent hemoglobin, the NPN 70 mg. per 100 cc. The urine was smoky amber, acid, specific gravity 1.010, albumin two plus, urobilin one plus, occasional fine granular casts, red and white blood cells. The icterus index was 10. The next day the NPN went to 300, the leukocytes were 51,000, the red blood count was 2.00 million with 50 percent hemoglobin and urinary findings unaltered, with a 24-hour output of only 100 cc. In spite of intensive therapy and the establishment of a diuresis, the patient remained critically ill for 2 more days. The azotemia persisted and the carbon dioxide combining power (determined for the first time) was 20 volumes percent.

Clinical improvement, which was first noted on the thirteenth day, continued. Uric acid and creatinine levels were elevated in proportion to the NPN. The leukocytosis became normal on the twenty-third day. Renal function tests during the last week of hospital stay demonstrated persisting impairment of function. The patient was considered recovered and was discharged on the forty-second day.

Nervous complications of sulphonamide therapy. *Lancet*, London, 2: 162-163, Aug. 9, 1941.

Since the introduction of the sulfonamides, the nerve lesions which may complicate the acute infections seem to have been less rare, presumably because more patients with severe infections now survive long enough to develop them. However, these nerve lesions must be distinguished from the peripheral neuritis which may be produced by the drugs themselves. Clinically, the course of the two is different. In the septic type the lesion is either a radiculitis, especially in streptococcal infections, or is confined to the ulnar or peroneal nerve, which becomes acutely painful and tender, with paresis of the muscles it supplies. The sulfonamides, however, produce progressive paresthesias of the extremities with muscular weakness beginning in the small muscles of the hands and feet and gradually spreading centrally accompanied by sensory and reflex loss; in one or two extreme instances there has been complete loss of power in all four limbs. The sulfonamide neuritis was originally described as a rare toxic effect of sulfanilamide, usually after considerable overdosage, the amount given ranging from 50 to as much as 130 gm. With the development of the sulfanilamide derivatives, particularly p-aminobenzenc-sulfondimethylamide, case-reports have been fairly frequent, and total amounts of only 12 to 30 gm. of this compound have caused the trouble. The etiology of the neuritis is not fully understood, but experiments in pigeons have shown that vitamin B₁ will prevent paralysis, and in patients undergoing sulfonamide therapy there is a decreased excretion of vitamin B₁. Unfortunately treatment of the neuritis with vitamin B₁ is only partly successful. All that can be done is to stop the drug and rest the affected parts with splints until the acute phase has subsided. When there are signs of returning activity, steadily increasing faradism with remedial exercise should be given. In severe cases, recovery is

slow but the ultimate prognosis is still good.

The pathology of the lesions has not been studied adequately in the human subject, but much has been learned from animal experiment. Chickens are peculiarly liable to have lesions of the central nervous system during sulfonamide therapy, and in them Beiter and his colleagues of Minneapolis have demonstrated myelin condensation with axon swelling from this cause. Sulfanilamide was found to be the least harmful to the central nervous system of the drugs studied the order of increasing toxicity being then sulfapyridine, sulfathiazole, and sulfamethylthiazole. In chickens it was possible to demonstrate selective variations in the concentration of different compounds in different parts of the central nervous system after treatment, and similar variations are probable in man. The human sciatic nerve may certainly show concentrations appreciably higher than those found in the blood, and if this is representative of other peripheral nerves the mechanism of neuritis becomes understandable. The importance of the selective distribution of sulfonamides between blood cells and plasma has been pointed out, and a study of the distribution in other organs seems worth attempting.

Some patients have had acute meningitis following intrathecal use of sodium sulfapyridine; and paralysis of the cauda equina, with slow recovery, has been reported after other soluble compounds administered in this way. Other patients have had injuries to the gluteal or sciatic nerve, particularly its external popliteal division, after careless intramuscular injections of sodium sulfapyridine, which may produce local necrosis. It is unwise to give more than 1 gm. in 33 1/3 percent solution into the buttock at any one time. If more must be given, it should be given intravenously.

Mental disturbance more pronounced than that commonly arising during acute fevers may be observed during sulfonamide therapy and may be a sign of

overdosage (Johnstone, D. F.; Forgacs, P.: *Brit. M. J.*, 1: 772, 1941). An extreme example of this was in the patient who had acute mania after he had been given 4 gm. of sulfapyridine every 4 hours for 3 days, by mistake. He recovered both mentally and physically on withdrawal of the drug. Less severe examples of confusion are sometimes seen after moderate dosages, indicating that the patients are sensitive to the drug. A peculiar form of delayed cerebral depression may follow any of the sulfonamides now in common use. This depression is characterized by inability to concentrate or add up simple sums, with loss of the fine coordinating power necessary for performing acts such as typing. The final prognosis of this is good. The amide of nicotinic acid may be effective in such cases.

Pemphigus foliaceus-like eruption following use of sulfanilamide and sulfapyridine. Max S. Wein and Eugene P. Lieberthal. *J. A. M. A.*, Chicago, 117: 850-852, Sept. 6, 1941.

A male patient of the Michael Reese Hospital, suffering from acute left otitis media and mastoiditis, was given sulfanilamide from Nov. 18 to 27, after which a generalized morbilliform eruption developed. (The dosage of the drug is not given.) Three days after the drug had been discontinued the eruption had practically receded and a simple mastoidectomy was performed. About Dec. 8 a generalized malodorous dermatitis with exfoliation developed. At readmission to the hospital he appeared acutely ill, and his skin presented a generalized light brown pigmentation with large, lakelike, moist exfoliation superimposed. During January and February he received a total of 500 cc. of human serum intravenously. There was constant improvement in his physical condition but several bullae appeared on his body. These ruptured, leaving raw, oozing surfaces. The patient was kept on supportive therapy and seemed to be making an uneventful recovery until May 20, when he died with severe dyspnea.

Changes observed at post mortem examination included abscesses of the left lung with peripheral bronchopneumonia; bronchopneumonia of the right lung; tuberculosis of the tracheobronchial lymph nodes; brown atrophy of the heart; pulmonary emphysema and edema; diffuse hemorrhagic cystitis; chronic hyperemia of the liver and kidneys; multiple, extensive decubital ulcers; meningeal hyperemia; a solitary hematoma of the liver.

The sulfonamides have great power to harm the patient, and there is necessity for the trained user of them to recognize the varied cutaneous pictures which indicate a toxic reaction, in order that the use of the drug may be promptly stopped.

Development of acute exfoliative dermatitis during administration of sulfathiazole. Mary Weinstein and Albert H. Domm. *J. A. M. A.*, Chicago, 117: 607-608, Aug. 23, 1941.

An acute exfoliative dermatitis developed in a Negro patient suffering from an atypical pneumonia after he had received in 2 days 15 gm. of sulfathiazole accompanied by equal amounts of sodium bicarbonate. He died on the ninth day after admission to the Philadelphia General Hospital. Autopsy revealed that almost the entire cutaneous surface of the body was affected, except the hands, forearms, feet and legs. The epiderm was exfoliated in great patches. Nikolsky's sign was present on regions of involvement. There were no definite blebs; it appeared that the epiderm had simply been loosened from the corium.

The abrupt onset of cutaneous involvement, increasing fever and progressive toxicity, together with the unusual dermatologic process, suggests that the case is an instance of acute exfoliative dermatitis due to sulfathiazole. Other than an overwhelming toxemia resulting from the widespread involvement of the skin, no satisfactory cause of death was found. It is of significance that this patient experienced a cutaneous rash in 1929 following intravenous therapy, presumably from arsphenamine, for "bad blood."

The potential danger of sulfathiazole

dermatitis should be kept in mind with the first appearance of cutaneous lesions. Withdrawal of the drug and forcing of fluids at the first sign constitute the safest procedure.

Sodium sulfathiazole: Its caustic action. Russell Fletcher. California & West. Med., San Francisco, 55: 94, Aug. 1941.

The author reports the case of a patient treated locally with sodium sulfathiazole for sinusitis, which illustrates the extreme danger of such use of the drug. The drug charred or burned the granulations and entire lining of the left antrum of the patient. Each time that it was given, the drug was allowed to escape immediately from the sinus through the nose and through a fistula into the mouth. If it had remained in the antrum, more serious complications probably would have resulted.

The sodium salts of the sulfonamide group are extremely alkaline, having a pH which ranges from 10 to 11. This is about as alkaline as arsphenamine, and it is well known that arsphenamine, because of its alkalinity, causes necrosis when it gets outside of a vein. Such solutions are extremely caustic and may do irreparable damage if they are instilled into tissues, sinuses, or any body cavity such as the pleural or peritoneal cavity.

Transitory myopia. A complication of sulfanilamide therapy. Samuel S. Blankstein. Am. J. Ophth., St. Louis, 24: 895-899, Aug. 1941.

Transitory myopia occurs largely from the local ocular disturbances such as trauma and iritis and from general systemic diseases such as diabetes. Drug therapy is an important etiologic factor in its production, especially from arsphenamine preparations and sulfanilamide.

Blankstein reports a case of transitory myopia following treatment with sulfanilamide. A white male, aged 34 years, was referred to him on September 6, 1939, because of blurring of vision of 19 hours' duration. His family physician had been treating him with sulfanilamide for a

gonorrheal urethritis during the past days. He was taking 40 grains daily 4 equal doses with an equal amount sodium bicarbonate. The response therapy was quite good. Repeated Wassermann examinations were negative. On September 5 there had been a sudden marked blurring of vision for distance to such a degree that he was unable to drive his car. He had never worn glasses and had never had any eye complaint. Examination showed that the unaided vision was 0.1 in the right eye and 20/30 in the left. There was good light perception and projection. The sulfanilamide was stopped immediately, and the patient was advised to drink a large amount of fluid. In the next 24 hours he developed a toxic dermatitis characteristic of that seen following sulfanilamide therapy. On September 12 the unaided vision in each eye was 1.2 and the accommodative power was 6.0 diopters.

The author says a study of the case ruled out ciliary spasm as a factor and led to the conclusion that the condition was more likely a reaction on the part of the lens either on an allergy basis or as due to a difference in the osmotic tension of the lens as compared to the aqueous produced by the unequal distribution of sulfanilamide within the eye.

Acute myopia induced by sulfanilamide. Report of a case. Bernard B. Friedman. Am. J. Ophth., St. Louis, 24: 935, Aug. 1941.

A white male, 29 years old, had been given a prescription for 150 grains of sulfanilamide to be taken in 20 hours. On the fourth day the patient came to the author with the complaint that his distance vision was considerably blurred. Examination revealed that the vision for distance was R. E. 20/80, L. E. 20/100. The pupils were slightly larger than normal but reacted promptly to light and accommodation. Two days later, when no more sulfanilamide had been taken, the vision was 20/20 in each eye without correction and the patient felt his vision had returned to normal. Several months later examination showed no changes.

The author concludes that acute myopia is another of the possible toxic manifestations of the ingestion of sulfanilamide. The use of medication with less toxic reactions is suggested in the treatment of diseases where sulfanilamide is not specifically indicated.

Problems in lymphogranuloma venereum. Marion E. Howard. *Internat. Clinics*, Philadelphia, vol. 2, New Series 4: 187-199, June 1941.

Among the many problems in venereal lymphogranuloma are the early diagnosis of the disease, when patients are infectious, and the best form of therapy for a particular case. One of the greatest needs is a clear understanding of the significance of a positive Frei test and the circumstances under which the test may be negative.

During the primary stage of the disease, the chills, fever, malaise, and joint pains are often lightly passed over by the patient as being due to the flu. It is during this phase that the infrequently seen or recognized primary lesion may be present. The Frei test is apt to be negative or doubtful and early diagnosis obscure. During the secondary stage, when regional lymph nodes are involved, the Frei test becomes positive, but in some cases not until there is beginning suppuration of the gland itself or involvement of the overlying skin. This necessitates repeating the skin tests in early suspicious cases where the results of the first tests are negative or doubtful.

Three cases are discussed. Because of the youth (17 years) of the first patient, the positive skin test to brucellergin, and the genital ulcerations being completely overlooked, the diagnosis of venereal lymphogranuloma was not made. Some months later this girl was the source of infection in the second case, and he, in turn, transmitted the disease to his wife, case 3. No data could be collected as to the incubation period in any of these cases. The period during which the patient with venereal lymphogranuloma remains infectious is, in all probability, a long one. In case 2 it was

not until a month after admission to the hospital and 6 weeks after the onset of acute illness that a Frei test was positive. How diagnosis can be established early in such Frei-negative cases is a question. Chemical studies on the blood and serum of these patients have demonstrated that there is a persistent hyperglobulinemia in most of them. This may be determined by the formol-gel test or the Takata-Ara test. While an increased globulin is not pathognomonic for venereal lymphogranuloma, in a patient with lymph node enlargement it should bring to mind such a diagnosis. False positive Frei reactions are not as a rule troublesome if attention is paid to the source, preparation, storage, and sterility of the antigen used. Case 3 was considered as a possible case of typhoid in a Frei-positive individual until repeated stool cultures failed to show typhoid organisms.

No specific therapy was employed in these early cases. Recently, semiweekly intravenous injection of Frei antigen and the oral administration of sulfanilamide have been advocated. Approximately 30 to 40 percent of cases with inguinal adenitis subside without suppuration and fistulas improve on bed rest or restricted activity alone.

Two cases are discussed in which surgery was repeatedly resorted to for rectal abscesses before venereal lymphogranuloma was suspected and Frei tests done. Howard believes that all cases of proctitis and colitis are worthy of a Frei test and careful proctoscopic and X-ray examinations; in many instances the patient may be saved inadequate treatment, recurrence, or even serious spread of the infection. The first step in the treatment of any rectal lesion should be directed toward determining the extent of involvement of the rectum and the activity of the lesion. The results with surgery in many instances have been poor. Since the disease tends toward cicatrization, in the absence of a specific therapy attention might better be directed toward improving the general physical condition of these patients with the hope of accelerating the natural processes of heal-

ing. Surgery may then be attempted at a later date if it is indicated.

The therapy of lymphogranuloma venereum. Robert Brandt and Robert B. Greenblatt. *South. M. J., Birmingham*, 34: 941-949, Sept. 1941.

The authors discuss the results of treatment of 202 patients who had venereal lymphogranuloma. The methods employed were: (1) Topical treatment (dusting powders, iontophoresis, cauterization, antiseptics), (2) surgical treatment, (3) proteinotherapy (including nonspecific proteinotherapy and convalescent serum), (4) vaccinothrapy, (5) chemotherapy, (6) physiotherapy. They state that topical treatment, beyond cleanliness and protection, is both unnecessary and ineffective. Only secondary fusospirochetosis must be so treated, preferably with a mixture of cod liver oil and zinc peroxide or with a solution of cod liver oil plus neoarsphenamine in glycerine. Buboos should not be incised, although the pus may be aspirated if necessary. Total extirpation of the glands is an effective way of terminating the entire infection, but this procedure requires long and expensive hospitalization, and lymphatic obstruction may follow. Milk or nonspecific vaccine injections have some effect on acute buboes but are ineffective in chronic lesions. Treatment with convalescent serum or whole blood is sometimes rather successful. In the experience of the authors, subcutaneous or intracutaneous vaccinothrapy with Frei antigen was effective only in the recent stages of the disease. In chronic manifestations it was not as effective. Intravenous administration of Frei antigen produced considerable improvement in three cases and slight improvement in three other cases. It resulted in subjective relief in one case of esthiomene, but it had no effect in one case of venereal lymphogranuloma combined with venereal granuloma.

Sulfanilamide, sulfabenamide (French preparation), sulfapyridine, sulfanilic acid, and sulfathiazole were the sulfonamides used in this series. The antimony

preparations fuadin and anthiomaline were used in some cases. The administration of sulfanilamide was relatively inexpensive, comparatively effective, and rather well tolerated. The effect of sulfabenamide was somewhat slower than that of sulfanilamide, but it was less toxic and could be used in prolonged treatment. Sulfapyridine was found to be unsuitable for ambulatory clinic patients because of disagreeable side effects. Sulfanilic acid was well tolerated, but it produced no beneficial results in recent cases, and it seemed to have little effect in chronic cases. However, Hebb, Sullivan, and Felton have reported excellent results from treatment with this drug in chronic cases over long periods of time. The authors have no final judgment concerning sulfathiazole. In a few cases with draining sinuses there was no remarkable cessation of the discharge.

The authors found the antimony drugs useless. Eight to 18 injections of fuadin or anthiomaline failed to induce any change in six patients with elephantiasis or chronic lymphadenitis. In one patient with venereal granuloma developing on an older venereal lymphogranuloma bubo, fuadin cured the venereal granuloma but left the fistulization unchanged. Fifty-six tablets of sulfabenamide greatly lessened the discharge from the fistulae in this case.

Roentgen-ray therapy was found to be of no use in chronic manifestations. In buboes, it sometimes hastened suppuration. The final results were less favorable than those obtained by chemotherapy or vaccinothrapy. For this reason, the treatment was carried out with a small number of patients, only.

According to Martz and Foote, long-wave diathermy is very effective in rectal stricture. In the authors' clinic, short-wave treatment was used. Almost immediate relief of pain or discomfort was the most striking effect of short-wave application, whether the coil or the rectal electrode was used. The authors do not yet know what permanent results may be expected from such treatment.

The authors summarize the results of treatment as follows:

1. **BUBO.** The acute bubo of venereal lymphogranuloma is profoundly influenced by chemotherapy with sulfanilamide and its derivatives and compounds. Late manifestations do not occur after intensive early treatment, but chronic lesions (especially rectal strictures) often develop without preceding acute manifestations. Vaccinotherapy is also effective in the acute stage, but to a lesser degree. Surgical procedures, except for aspiration of pus, are rarely indicated.

2. **ULCERATION AND ELEPHANTIASIS.** Ulcerative and hyperplastic lesions are less favorably influenced than buboes. Those of short duration usually yield to prolonged chemotherapy, possibly reinforced by vaccinotherapy or physiotherapy. Chronic ulcerations and elephantiasis are, however, resistant to therapy. Chemotherapy is often effective in relieving pain and discharge, and may combat progression, but only occasionally does it produce a definite cure. Symptomatic improvement may also be accomplished by intravenous vaccinotherapy or physiotherapy. The removal of hypertrophic tissue usually allows good and often persistent results, especially if combined with chemotherapy.

3. **RECTAL STRICTURE.** In patients with rectal stricture, chemotherapy often relieves pain, rectal leukorrhea, and general complaints. Stenosis is relieved by mechanical dilatation, and chemotherapy is highly recommended. Long-wave or short-wave diathermy has a favorable effect on the inflammatory process and allows the stenotic lumen to soften. Here, too, the combination with mechanical dilatation is recommended.

Patients treated in the acute stage of venereal lymphogranuloma may expect complete healing. The treatment of neglected lesions or those developing without a preceding acute stage is less promising, but the therapeutic procedures available at present are sufficient to lessen many complaints and to create a tolerable situation for most of the patients (much

more so than could have been provided in the past).

Influence of various therapeutic measures on periodic heart block associated with Cheyne-Stokes respiration; a case report. Henry Miller and Frank T. Fulton. *Ann. Int. Med.*, Lancaster, 14: 2296-2306, June 1941.

A 56-year-old Negro man was admitted to hospital on October 9, 1938, complaining of exertional and paroxysmal dyspnea, cough, and insomnia. There was a history of an untreated penile sore about 20 years previously. A diagnosis of syphilitic aortitis was made. The patient improved rapidly with bed rest, digitalis, and routine cardiac care, and he was discharged improved 11 days later. An electrocardiogram showed marked left axis deviation, prolonged P-R time up to 0.24 second and diphasic T-waves in lead I.

On November 13, 1938, he was readmitted to the hospital in an attack of acute pulmonary edema. He again improved rapidly with oxygen, bed rest, digitalis, and sedatives and was discharged 2 weeks later. An electrocardiogram showed a more deeply inverted T₁, a diphasic T₂, and marked left axis deviation. In the precordial lead the T-wave was inverted.

Following discharge, the patient was fairly comfortable with greatly restricted activity and 1½ grains of digitalis per day until 12 days prior to the third admission to the hospital, at which time he again began to have attacks of nocturnal dyspnea. When admitted to the hospital this time he had Cheyne-Stokes respiration. The pulse became slow during the apneic periods and increased during the hyperpneic phases. The veins of the neck were congested and showed expansile systolic pulsations. There was marked systolic pulsation of the carotid vessels. The pupils were unequal and fixed to light; the fundal vessels were moderately arteriosclerotic. A heaving elevation of the entire chest synchronous with each heart beat was evident. Resonance was diminished over the lower third of both lungs posteriorly and over these areas

moist râles were heard. The outermost point of cardiac action was seen and felt in the sixth left intercostal space in the midaxillary line as a systolic heave of marked amplitude. The right cardiac border was percussed 5 cm. from the mid-sternal line in the fifth interspace. There was a moderately loud systolic and blowing diastolic murmur best heard at the base but transmitted over the entire precordium. The pulmonic second sound was accentuated. During apnea, the rate was about 40 per minute, and during hyperpnea, 78 per minute. The peripheral vessels were moderately thickened; and Corrigan pulse, capillary pulsations, and Duroziez's signs were present. The blood pressure was 154/60. Roentgenograms of the chest showed the cardiac silhouette increased in all diameters, especially in the region of the left ventricle. There was an increase in the supracardiac dullness, especially in the region of the ascending portion of the aorta, consistent with the diagnosis of syphilitic aortitis or aneurysm of the aorta. The findings in the lungs were due to congestive changes. The Wassermann and Kahn tests were positive on three occasions. An electrocardiogram showed a partial heart block in leads I and IV and in leads II and III, a complete auriculoventricular dissociation with bigeminy due to alternate ventricular extrasystoles. The Q-R-S complexes were slurred and showed left axis deviation. In leads I and II the S-T segments were depressed and the T-waves diphasic. In the precordial lead, the T-wave was still inverted. The diagnosis was syphilitic heart disease, cardiac hypertrophy and dilatation, aneurysm of the ascending aorta, aortic insufficiency, transient heart block, class III.

According to the authors, this case afforded an unusual opportunity to study factors influencing the occurrence and disappearance of heart block associated with Cheyne-Stokes respiration. Digitalis, morphine, and carotid sinus pressure, which are known to increase vagal tone, either induced or accentuated the heart block, while atropine abolished the block. This confirmed the vagal origin

of the periodic variations in rhythm. Epinephrine, 50 percent glucose, and paredrine failed to modify the block. This supports the view that the vagus is the mechanism by which the block was produced.

Contrary to usual experience, caffeine sodiobenzoate was the only measure which restored normal breathing and coincidentally abolished the transient heart block in this patient. Whether this was due to stimulation of the respiratory center is problematical. Oxygen administration resulted in subjective improvement without affecting the periodic respiration, while aminophyllin, except for a slight modification of the type of respiration, was ineffectual. The failure of mecholyl to reproduce the heart block was attributed to the individual variation in response to the drug.

The authors discuss the literature on, and their own experience with, the following drugs and therapeutic measures: (1) Atropine. (2) theophylline-ethylenediamine, (3) caffeine sodiobenzoate, (4) morphine, (5) acetyl-beta-methylcholine chloride (mecholyl), (6) digitalis, (7) carotid sinus stimulation, (8) oxygen administration.

PATHOLOGY

The aortic valvular lesion associated with the Austin Flint murmur. Benjamin A. Gouley. *Am. Heart J.*, St. Louis, 22: 208-218, Aug. 1941.

An explanation of the Austin Flint murmur that is acceptable to many clinicians is that blood regurgitating through a damaged aortic valve strikes against the anterior mitral curtain and pushes it laterally into the auriculoventricular blood stream, thus creating a functional obstruction at the mitral valve.

In a series of 10 patients who had Flint murmurs incidental to aortic regurgitation, a characteristic deformity of the

right aortic leaflet was found at necropsy. This consisted of a concave, cup-shaped efficiency of the inner portion of the leaflet, so situated as to divert the regurgitating blood toward the lower portion of the anterior mitral curtain. The latter showed on its ventricular aspect thickening which was interpreted as frictional sclerosis. The posterior aortic leaflet was normal in some cases. Gouley does not attempt, on the basis of this small series of patients, to exclude posterior leaflet lesions as occasional factors of importance. His experience indicates, however, that they are uncommon. The majority of the patients studied had syphilitic cardiovascular disease; one case had complicating subacute bacterial mitral endocarditis and in two the aortic lesion was due solely to rheumatic disease. It appears that some destructive process incidental to infection, usually syphilitic, plays an important role. Gouley has previously pointed out that destruction of the supporting fibro-elastic "basket" of the right anterior aortic leaflet by syphilis was a determining factor in the subsequent valvular deformity. It is probable that a similar inflammatory process is involved in the localization and development of the valvular deformity of the Flint murmur.

In 4 of the 5 cases discussed at length here was syphilitic involvement.

LABORATORY RESEARCH

The vesicular test. Diagnostic method of infection by poradenic (lymphogranuloma inguinale) virus. Carlos Ottolina. *Am. J. Trop. Med.*, Baltimore, 21: 597-602, July 1941.

Frei's test links many different pathologic processes which are classified as the venereal disease. It has been suggested that the infection by poradenic virus should be considered a general dis-

ease with three periods, like syphilis, and with anatomic changes more or less limited to the rectogenital area, although extragenital localizations have been described.

The study of patients suspected of poradenic virus infection is sometimes difficult because the Frei antigen is not always at hand; the buboes may be scarce and the activity of the antigen is limited. To overcome these difficulties, antigenic animal sources have been created by artificial infection of the market ape and white mouse. Ottolina has found the ape antigen not so reliable as the human antigen. Since peculiarities of the classic Frei test sometimes leave the observer perplexed, several workers have been trying to find a new diagnostic method for the poradenic virus infection. Ottolina focused his attention on the cerebrospinal fluid in his search for a human antigen easy to obtain, aseptic, and containing a small amount of albumin.

Spinal puncture and vacuum concentration of the fluid were carried out under aseptic conditions. If the fluid obtained by reducing 10 cc. to 1.5 cc. (concentration No. 1) is injected intradermally, a vesicle appears 24 hours later at the point of injection. The shape of the vesicle may be ovoid, circular, or triangular, but there is a definite trend toward the hemispheric form. The dimensions vary greatly. The blister skin always has a darker shade than the surrounding skin. The fluid in the blister shows a light tension 24 hours after the injection; after 4 or 5 days the blister is only a pigmented spot about 2 mm. in diameter. The volume of the vesicular fluid is about 0.05 cc. A standard technic was adopted, using the concentration of the cerebrospinal fluid obtained by reducing 10 cc. of fluid to 2 cc. (concentration No. 2) and an intradermal injection of 0.3 cc.

In the Frei-positive cases with anatomic changes, i. e., proctitis, rectal stricture, Jersild's syndrome (5 cases) the vesicular test was always positive. The Frei-negative cases, with anatomic changes of marked rectal stricture (2 cases), showed the vesicular test also

negative. In the Frei-positive cases without rectogenital changes (5 cases), the vesicular test was positive. Similarly concentrated cerebrospinal fluid obtained from Frei-negative men and injected into Frei-positive patients did not produce any blister, papule, or erythema. Frei-negative men without rectogenital changes (8 cases) did not show any reaction to fluid obtained from Frei-positive or Frei-negative subjects.

Other concentrations less strong than the No. 2 sometimes produced the reaction. The standard amount of 0.3 cc. and also 0.2 cc. always provoked the reaction; if 0.1 cc. was injected the test proved negative. The life of the antigenic power in the concentrated fluid has not been definitely determined. A temperature of 56 degrees maintained for a half hour does not alter the antigenic power of the concentrated fluid. An autoreaction is possible.

Ottolina feels that these results warrant confirmation by other workers.

The therapeutic activity of the organic arsenical compounds in syphilis of rabbits in relation to the urinary excretion of arsenic. John A. Kolmer, Herman Brown and Anna M. Rule. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 486-495, July 1941.

The authors report the results of an investigation conducted with arsphenamine, neoarsphenamine, sulfarsphenamine, and bismarsen in an attempt to determine the urinary excretion of arsenic in relation to the biologic cure of rabbits with acute syphilitic orchitis as well as in relation to the prevention of syphilitic orchitis in these animals.

A summary of the results of the investigation is as follows:

1. Single intravenous injections of arsphenamine in dose of 0.012 gm. and of neoarsphenamine in dose of 0.016 gm. per kg. resulted in the biologic cure of rabbits with acute syphilitic orchitis with a total daily urinary excretion of arsenic varying from 0.15 to 0.38 mg. over the first 3 days following treatment.

2. With sulfarsphenamine, the minimum curative dose was 0.024 gm. by intramuscular injection with the total daily excretion of 0.65 to 2.58 mg. of arsenic over the same period of time.

3. With bismarsen, the minimal curative dose was 0.012 gm. by intramuscular injection, accompanied by the total daily excretion of 0.42 to 1.31 mg. arsenic over a period of 3 days in which case the lower excretion of arsenic in relation to cure was evidently due to bismuth.

4. Biweekly intravenous injections of 0.002 to 0.004 gm. arsphenamine and 0.003 and 0.008 gm. neoarsphenamine per kg. for 3 weeks did not effect the biologic cure of rabbits with total daily urinary excretions of arsenic varying from 0.02 to 1.18 mg. over the period of treatment.

5. Biweekly intramuscular injections of sulfarsphenamine in dose of 0.008 gm. per kg. for six doses resulted in biologic cure accompanied by a total daily urinary excretion of 0.12 to 1.18 mg. arsenic over the period of 3 weeks.

6. The biweekly intramuscular injection of bismarsen in dose of 0.003 gm. per kg. for six doses resulted in biologic cure with a total daily excretion of 0.02 to 0.54 mg. arsenic over the period of treatment.

7. Single intravenous injections of arsphenamine in dose of 0.012 gm. per kg. did not protect rabbits against infection when inoculated intratesticularly with *T. pallidum* on the same day and 1, 2, 4, and 10 days later with total urinary excretions of 0.24 to 0.48 mg. of arsenic on the days of inoculation.

8. The single intravenous injection of neoarsphenamine in dose of 0.024 gm. per kg. protected a rabbit against infection when inoculated intratesticularly with *T. pallidum* on the same day with a total urinary excretion of 0.53 mg. arsenic. But rabbits inoculated 1, 2, 4, and 10 days after this treatment developed syphilitic orchitis with total urinary excretions of arsenic varying from 0.5 to 0.9 mg. on the days of inoculation.

9. The single intramuscular injection of bismarsen in dose of 0.018 gm. per kg. protected rabbits against infection when

inoculated intratesticularly with *T. pallidum* on the same and the following day, when the urine showed a total urinary excretion of 0.42 to 0.46 mg. of arsenic. Rabbits inoculated 2, 4, and 10 days after this treatment developed syphilitic orchitis with total urinary excretions of 0.3 to 0.72 mg. of arsenic on the days of inoculation.

10. The question of total urinary excretion of arsenic in relation to the treatment of human syphilis with arsenical compounds is discussed. Urinary estimations of arsenic in relation to dosage may be of some value in human beings receiving arsenical treatment.

The effect of alkali on crystalluria from sulfathiazole and sulfadiazine. Leon Schwartz, Harrison F. Flippin, John G. Reinhold and Albert H. Domm. *J. A. M. A., Chicago, 117: 514-515, Aug. 16, 1941.*

Hematuria, oliguria, anuria, pain in the loin and uroliths associated with the use of sulfapyridine or sulfathiazole have been reported in the literature. These renal complications are due, in part if not entirely, to the presence of sulfapyridine or sulfathiazole crystals in the urinary tract. They have sometimes necessitated the discontinuance of the chemotherapy at a time when treatment was most desired. A daily output of at least 1,200 cc. of urine has previously been recommended in order to facilitate the excretion of these compounds.

A study of the urine from 50 adult patients receiving sulfathiazole in the treatment of pneumonia and 50 receiving sulfadiazine has been made by the authors. They examined 180 samples of urine from patients who had received alkali during treatment and 110 samples from patients to whom sodium bicarbonate was administered in an amount equal to that of the drug. It was found that the incidence and number of crystals of the drug found in the urine samples were distinctly less in the group which had received alkali together with either sulfathiazole or sulfadiazine. Patients receiving sulfadiazine showed fewer crys-

tals in their urine than did those receiving sulfathiazole.

The authors conclude, therefore, that it is advisable, in order to decrease the incidence and number of crystals of these drugs in the urine, to administer an alkali with sulfathiazole and possibly also with sulfadiazine.

A rapid bedside test for the concentration of sulfanilamide, sulfapyridine and sulfathiazole. A. G. Sheftel. *J. A. M. A., Chicago, 117: 439-440, Aug. 9, 1941.*

Sheftel describes a new, rapid, bedside method for the determination of sulfanilamide, sulfapyridine and sulfathiazole, a modification of the Marshall method, which has the following advantages: All reagents are stable, in tablet form. The only pipette required is one for collecting blood. Only 0.1 cc. of blood for sulfanilamide test, and 0.2 cc. for the sulfapyridine and sulfathiazole tests are required. A special colorimeter consists of a lucite wedge mounted on a frame on which there is an attachment to hold the test tube containing the substance to be examined.

The blood to be tested is collected in a test tube which has been filled with water to the upper mark. The four reagents in tablet form are added in the proper order, shaking the tube and letting it stand for a half minute between the additions. The tube is then inserted into the clip of the colorimeter, and the window is slid up or down until the color of the tube matches the lucite wedge standard. The concentration is then read, expressed in milligrams per hundred cubic centimeters of blood on the scale.

Leprosy: Complement fixation with Gaetgens' spirochete antigen compared with standard Wassermann and Kahn tests. D. W. Patrick and D. M. Wolfe. *Pub. Health Rep. Washington, 56: 1757-1759, Aug. 29, 1941.*

In 1939 Capelli performed complement fixation tests on the serums of 24 leprous patients, employing Gaetgens' phenolized cultures of *Treponema pallidum* (palligen) as antigen, and compared the re-

sults with those obtained with the Wassermann procedure and the Meinicke flocculation test. He reported that with Gaehtgens' test none of the serums gave a positive result with the exception of one case which was considered to be syphilitic. The Wassermann reactions were positive with 66 percent and the Meinicke with 39 percent of the serums.

The authors have carried out a similar study with serums from 94 patients in Kalihi Hospital, Honolulu, who were considered nonsyphilitic after careful study. Gachtgens' original procedure was not followed exactly because it was considered more desirable to use the technic of the standard Wassermann (Kolmer) test, merely substituting the palligen for the Kolmer antigen. Gaehtgens' recommended dose (0.25 cc. of equal parts of stock palligen and 0.3 percent phenolized physiologic salt solution) was used. Serum dilutions of 1:5, 1:10 and 1:20 were examined, and the standard complement fixation procedure was closely followed. The final result of each serum was obtained by totaling or summarizing the results of the 3 serum dilutions.

The results obtained are given in a table. It is shown that with the spirochete complement fixation reaction, the percentages for the maculo-anesthetic, bacteriologically negative cases, the maculo-anesthetic, bacteriologically positive, and the nodular type are 5.9, 3.3, and 10.5 respectively; for the maculo-anesthetic, bacteriologically positive, and nodular cases, the percentages were 10 and 70 for the Wassermann test, and 16.6 and 66.1 for the Kahn (no cases of the maculo-anesthetic, bacteriologically negative type were tested by the Wassermann or Kahn tests). Therefore fewer positive results were obtained with the spirochete complement fixation test than with either the Wassermann or Kahn—7.4 percent with the former and 38.3 with each of the latter; also more positive results were obtained with the serums of the nodular cases than with those of the maculo-anesthetic cases.

PUBLIC HEALTH ADMINISTRATION

Problems of the Negro in the venereal disease control program. Harold Whitted. J. Nat. M. A., New York 33: 168-170, July 1941.

Nearly 8,000,000 (30 percent) of the population of the South are Negroes. About 70 percent of the South's Negro population is rural. The author believes that the major problem of the venereal disease control program in the South is in the rural farm territory.

In 13 southern States, Negroes make up a larger percentage of the farm youth than of the nonfarm youth (census 1930). In Arkansas, Mississippi, and South Carolina, Negro youth comprise more than 40 percent of all farm youth. In two additional States—Georgia and Louisiana—more than 40 percent of the farm youth are Negroes. It is a notorious fact that these farm youths are less conversant on the cause, mode of spread, and modern methods of treatment of the venereal diseases. In the early 1930s (and conditions today are about the same) at least 900,000 Negroes of high school age were not in school. In two States—Arkansas and Mississippi—only 4.7 percent of the Negro population of high school age actually enrolled in high school. In five other southern States the percentage was below 10. In the southern States there were 230 counties having a population of 159,000 Negroes 15 to 19 years of age which did not have high school facilities for Negro pupils within their boundaries. In these same States there were 195 more counties with nearly 200,000 Negroes of high school age which did not have a 4-year high school for Negroes within their boundaries. It is an established fact that ignorance and poverty lead to a high incidence

venereal diseases. In contrast, recent studies have shown that the incidence of venereal disease in those who have had the privilege of attending high school or college is decidedly lower. In schools young people have greater access to medical advice on health in general and on sex and parenthood. Any attempt to bring the standard of Negro education up to the national average would aid greatly in the venereal disease program.

In the rural sections of the South, approximately 85 percent of Negro babies are delivered by midwives. The Negroes in this area are generally too poor to afford a physician, so they are forced to hire midwives, whose rates are much lower. Many of these midwives are illiterate and superstitious. They do not understand the importance of determining the existence of venereal disease in the mother. This fact is one of the reasons why the high stillbirth rate has continued to add much to the problem of control of congenital syphilis in these rural areas. With the improvement of health services, including free venereal disease clinics, and, if needed, traveling clinics for those who live long distances, fewer children in the South would die from the effects of syphilis.

The treatment of venereal diseases is generally an expensive item. The per capita gross farm income in the southeastern states in 1930 (with the exception of Florida) ranged from \$177.00 in Arkansas to \$172.00 in Virginia. It was not so low in any other part of the country. According to the results of a survey conducted by the Bureau of Home Economics of the U. S. Department of Agriculture, Negro families in 34 villages of Georgia and Mississippi spent an average of \$11.00 for medical care during an entire year. Many of these families go an entire year without the services of a physician. This means much unnecessary suffering not only for those infected with the venereal diseases but also for those with other types of disease. On such incomes these people cannot afford treatment from a private physician. It is essential that adequate and free clinic service be avail-

able in order that the venereal diseases may be controlled.

In the so-called free clinics in which the clinician receives a certain salary for his services to the local community, the clinician is usually required to be a member of the local county medical society. Negro physicians are not permitted to become members of such societies. Thus, they are disqualified as clinicians in the free clinics. The existence of such conditions does not foster cooperation between medical groups and does not work for the success of the venereal disease control program. Adequately trained Negro personnel should be employed to carry on this important work.

To achieve the goal in venereal disease control, serious national and local cooperation will be required. The fundamental problems of education of the rural Negro, prenatal examination and treatment, adequate free and traveling clinics for the indigent, and the employment of Negro clinicians will have to be solved. In many cases, the life and minds of the people must be freed from a prudish refusal to face facts. In all deliberations the aim and method must be governed by the thought of preserving the health of the people of the Nation. It is not a disgrace to be infected with a disease, but it is a reproach to the Nation to deprive the people of knowledge and modern medical aids which combat disease.

The Cleveland venereal disease program. E. J. Braun and R. N. Hoyt. *Bull. Acad. Med., Cleveland*, 26: 7-8, 13, Aug. 1941.

The Division of Health of Cleveland has always recognized the importance of adequate control of the venereal diseases, and has for years carried on this activity as a subdivision of the Bureau of Contagious Diseases. The central office for this activity is the diagnostic clinic at the city hall and a branch of the same at the central police station. The latter is limited to vice cases and other medicolegal cases. Close cooperation is maintained with all local and

national agencies, treatment clinics, and the medical profession.

The diagnostic clinic serves as an examining clinic and a clearing center for the public and the medical profession. Here persons come of their own volition to seek a diagnosis or advice, or are referred by physicians, clinics, or other agencies for the same purpose. Delinquents, contacts, and sources of infection are also examined at the diagnostic clinic, and are referred by physicians, clinics, hospitals, medical and social agencies, and out-of-town public health or other agencies. The division of health is not engaged in the active treatment of syphilis or gonorrhea. All persons requiring treatment are referred to a clinic or a physician.

A venereal disease register is maintained at the diagnostic clinic. This is a card index file of all new cases reported to the division of health by clinics, physicians, and hospitals. These morbidity statistics aid in studying the trend of disease incidence from year to year, as well as in furnishing other useful and important data. The original physician's venereal disease report is forwarded to the State Department of Health at Columbus. Physicians are required by law to report cases of venereal disease. Since the private physician diagnoses and treats over half the new cases occurring in Cleveland, it is clear that the success or failure of any control program depends on his cooperation with the division of health.

The control of syphilis through case-holding and case-finding among dispensary patients has reached a relatively high degree of perfection. Through special venereal disease nurses cooperating with the hospital dispensaries, patients are kept under treatment much longer than heretofore, and many new cases are found through contact follow-up. It is hoped that soon the private physician will cooperate in this manner, and that he will tolerate epidemiologic follow-up by the nursing staff as in the case of tuberculosis, typhoid fever, and other communicable diseases. The following free services are available to physicians in

Cleveland: (1) Consultation; (2) laboratory—blood tests, spinal fluid tests, smear examinations, dark-field examinations; (3) free drugs—mapharsen, neosalvarsan, tryparsamide, and bismuth subsalicylate; (4) follow-up services; (5) educational activities—literature, pamphlets, lectures, etc. In return for these free services the private physician should cooperate in the venereal disease control program.

Although the apprehension and control of prostitutes is a police matter, the Ohio State law empowers the local health authorities to examine and, if necessary, quarantine all persons arrested for vice offenses. In Cleveland all such persons are examined daily. About 50 percent of new offenders have infectious syphilis or gonorrhea. Old offenders have usually had syphilis and are not infectious, either having been cured or being still under treatment and on probation. Persons with open infectious syphilis are quarantined in the City Hospital and after release are treated at a clinic or by their private physician. Patients with early latent syphilis are quarantined in the hospital ward of the Women's Correction Farm at Warrensville, and later released to a clinic or a private physician. Uncomplicated cases of gonorrhea are quarantined at Warrensville, complicated cases at City Hospital.

Results of blood tests among draftees reveal about 2 percent positivity among the white men and 18 percent among Negro men.

On August 15, 1941, the recently enacted marriage law amendments go into effect, requiring blood tests for syphilis before marriage in Ohio.

Incidence of venereal diseases. Brit. M. J., London, 2: 208, Aug. 9, 1941. Also, **Present position of venereal disease.** Lancet, London, 2: 136-137, Aug. 2, 1941.

Since the outbreak of the War in England the incidence of venereal diseases has not increased to anything like the extent that was feared. A discussion on this subject arranged by the Medical So-

ciety for the Study of Venereal Diseases on July 26 brought out the unanimous view that while there had been some increase, it was very slight compared with the experience of previous wars.

Colonel Harrison showed that in 1939 the number of cases of early syphilis admitted for the first time at civilian centers in England and Wales was 4,986, a decrease of 45 percent since 1931 and less than a third of the number in 1920. The death rate from syphilis in infants fell from 2.03 per 1,000 in 1917 to 0.2 per 1,000 in 1939. The admission rate for syphilis in the Navy stationed at home fell from 8.1 per 1,000 per year in 1921 to 1.96 in 1936, the latest year for which published figures were available. In the Army at home, the syphilis rate fell from 9.8 per 1,000 per year in 1921 to 0.9 in 1937. In the Air Force during the same period, the rate for primary and secondary syphilis fell from 4.1 to 0.5. The higher rates in stations abroad suggest that the decline is some index of the improvement in the position at home.

Returns from civilian clinics indicated that from the outbreak of the War to the end of March 1940, the fall in the syphilis rate did not continue. Colonel Harrison estimated that syphilitic infections in men had increased in England and Wales in 1940 by about 27 percent and that the total increase in both sexes was about 23 percent.

Civilian cases of gonorrhea have been fewer than before, but when service cases were added, the total number of cases in men showed an increase of 9 to 10 percent. Colonel Harrison was disturbed to find that the treatment centers had treated fewer women in 1940 in spite of the clear evidence of increased incidence in men. However, sulfonamide treatment of gonorrhea has made recourse to private practitioners so much more common than before, that clinic statistics for the disease are now a very imperfect indication of incidence and comparisons with previous years are fallacious.

From October 1940, the Ministry of Health had refunded local authorities three-quarters of the approved cost for

new treatment facilities; 16 new centers were being set up as a result of this offer and 14 county authorities were making arrangements with practitioners to treat patients in their surgeries in areas where the amount of disease did not justify the establishment of a clinic.

Other speakers in the discussion supported the evidence of only a slight increase in venereal diseases except in the ports much frequented by foreign seamen, where a substantial rise had been noted locally. In the Army at home, the incidence had been about uniform week by week, and the total venereal disease rate in the Army fell from 11.3 per 1,000 in 1938 to 8.7 per 1,000 in 1940 and 8.4 per 1,000 in the first 5 months of 1941. The ratio of gonorrhea to syphilis has remained steady at 8 to 1. Everything possible has been done to make sure that venereal diseases are treated as far as possible like other diseases. In the Navy, it was stated, the present return of syphilis is the lowest on record. The Royal Air Force can also claim a very low incidence of both syphilis and gonorrhea, the total ratio being 6.3 per 1,000. The amount of venereal diseases among uniformed women was only 6 in a personnel of 16,000. There is much cause in this survey for thankfulness for the results achieved in the past quarter of a century, but no excuse for slackening of effort if the ground won is to be maintained.

The rural areas need more official attention, for soldier's wives are becoming infected and both knowledge and sympathy are required for the organization of rural clinics. A very small proportion of infections in the Army were due to professional prostitutes (6 percent), 80 percent were due to amateurs, and a surprising proportion of 14 percent were marital in origin. Even in country districts the "vicious amateur" forms a dangerous focus of disease and remains impervious to reason and education. Members of the discussion group seemed to be agreed that steps should be taken toward compulsory notification or treatment of recalcitrant contacts. However, it was pointed out

that such compulsion has been vigorously opposed in the past, partly because such a suggestion recalled the "ill-inspired" Contagious Diseases Acts and Regulation 40D of the last War, and partly because it appeared impossible to devise a scheme equitable for both sexes and free from danger of injustice to individuals. It was feared that there would be a public protest if there was discrimination against the female partner, and that there would be danger of malicious accusations.

Inwood House, New York—107th Annual Report, January 1, 1940 to December 31, 1940. New York, 16 pages.

In 1932 the Committee on Unmarried Mothers of the Welfare Council of New York made a survey and found that a home was needed to shelter and treat the unmarried, pregnant girls who had contracted venereal disease. Treatment of the girls in early pregnancy saves their babies from congenital syphilis. Continued treatment cures the girls and protects the community.

During 1940, 56 girls were referred to Inwood House by clinics, social agencies, and private sources. A few Negro girls were accepted as their need was urgent. The girls were accepted regardless of creed. Of the 56 girls, 2 were under 16 and 35 were under 21 years of age. The staff at Inwood House helped these girls make plans for a new life in the community and saw that their babies were protected and cared for in a good environment. Social workers secured an intensive history of each girl, so that her problems could be understood. An after-care committee, composed of members of the board and staff, met every 2 weeks to formulate plans for mother and child. The interest of this committee continued as long as the girl needed help. Each girl and baby was given a complete physical examination on admission, and special attention was given to the correction of defects in vision, hearing, dental, and other conditions.

Of the new girls, 15 had syphilis, 32 had gonorrhea, and 2 had both syphilis and gonorrhea. Of the 31 babies, 16 were

born of syphilitic mothers, but only 2 had congenital syphilis. The majority of these syphilitic mothers had not been given treatment before the fifth month of pregnancy. Treatment before the fifth month is important if the babies are to be born free of the disease. Nevertheless, due to the intensive treatment these girls received during their last months of pregnancy, most of their babies did not have the disease.

A weekly average of 15 girls and 4 babies were under treatment for syphilis, the number rising at times to 21 girls and 5 babies. There were 32 girls with gonorrhea who were treated at Inwood House until cured.

The total number of treatments given included 464 intravenous injections of neoarsphenamine, 119 intravenous injections of mapharsen (to those who could not tolerate neoarsphenamine), and 314 intramuscular injections of bismuth to the girls; and 178 intramuscular injections of bismarsen to the babies. All of the syphilitic girls were given spinal fluid examinations while in Inwood House in order to exclude neurosyphilis. The babies had roentgenograms taken at Bellevue Hospital for changes in the long bones. The New York City Board of Health furnished the drugs and performed the laboratory tests.

Psychologic tests were given to mothers and babies. Each girl was examined with a full battery of tests, including the revised Stanford-Binet, performance test, educational tests, and tests for special abilities. The following results were noted: 14 percent of the girls had superior intelligence, with I. Q. ranging from 110 to 143; 36 percent had normal intelligence, with I. Q. ranging from 95 to 105; 32 percent were in the dull normal group, with I. Q. ranging from 80 to 95; 18 percent were borderline and mental defectives.

The psychiatric study showed that three of the girls were psychotic, five were psychoneurotic, seven were neurotic (anxiety type), two had schizoid personalities, one was an epileptic, and six were aggressive behavior problems. The re-

remainder were fairly normal persons whose difficulties were largely environmental.

In addition to medical care, the young mothers were given sympathetic guidance in the care of their babies. An effort was made to prepare them for motherhood and its responsibilities. The girls lived a wholesome, simple life with good substantial food and moderate recreation. The holiday seasons were observed with appropriate celebrations. Each girl attended the church of her faith and an effort was made to help her spiritually. Each girl had a small room with a crib for her child. The girls were trained in housework and some were taught clerical work with practice on typewriters. All the girls were in a sewing class where garments were made for themselves and their babies.

In addition to the girls receiving care in Inwood House, 74 girls and 32 babies were carried under supervision and after-care from other years. Many of these girls came regularly for treatment and many returned for advice and friendly visits.

The babies who needed further treatment were brought to the Home by the mother or by the foster mother with whom the child was boarding.

The Federation of Protestant Welfare Agencies has studied for several years the programs of agencies dealing with unmarried mothers and finds that one outstanding need for the care of this group is a foster home program. The Federation has recommended that Inwood House is especially well equipped to develop this project. The Martha Mertz Foundation, whose funds are now available for the care of unmarried mothers, has offered to make the initial grant to start this program.

Inwood House is one of the agencies cooperating in the observance of Social Hygiene Day, under the auspices of the New York Tuberculosis and Health Association

(in February of each year). It has a membership in the Federation of Protestant Welfare Agencies, the Federation of Jewish Philanthropic Societies of New York, the New York Welfare Council, and the Social Work Publicity Council. It is also a participant in the Greater New York Fund.

Inwood House was founded in January 1830 and incorporated in 1851. In 1851 it was called "The New York Magdalen Benevolent Society." In 1913, the name was changed to "New York Magdalen Home," and in 1917 to Inwood House.

Public health service to fight venereal disease. Medical preparedness. J. A. M. A., Chicago, 117: 537-538, Aug. 16, 1941.

A venereal disease control program in areas of military and defense industry concentration has been approved by the President as a unit of the Work Projects Administration national defense research and records assistance project, for which an allocation of \$5,015,864 was made several months ago. The U. S. Public Health Service will act as official sponsor.

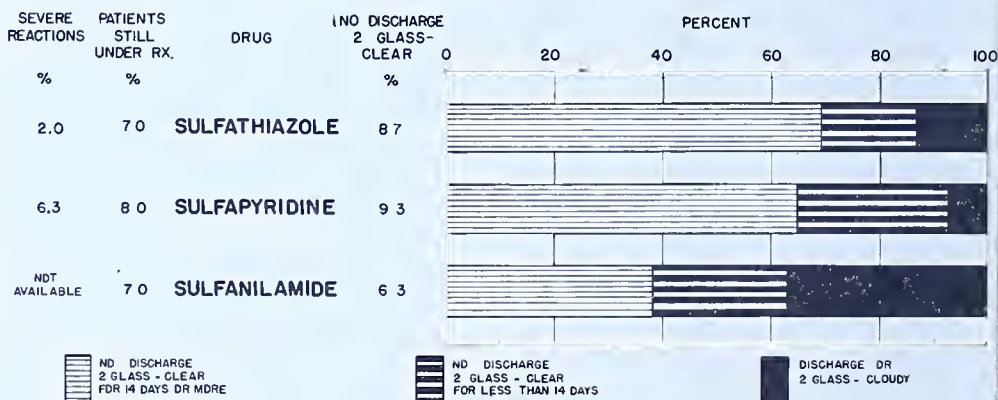
The purpose of the program is to provide assistance to State and local health authorities in (a) bringing under immediate treatment selectees who have been rejected or deferred because of syphilis or gonorrhea, (b) tracing the sources of infection, (c) placing treatment facilities for gonorrhea on a par with those for syphilis, and (d) establishing emergency venereal disease control programs in "boom" towns where regular public health facilities are insufficient to cope with the problem.

WPA workers have engaged in venereal disease control work in many parts of the country during the past 6 years. A recent survey shows that about 4,000 project employees in 33 States and the District of Columbia have assisted in the operation of 431 public clinics for the treatment of venereal diseases.

RAPID APPRAISAL OF SULFONAMIDE DRUGS IN THE TREATMENT OF GONORRHEA IN THE MALE

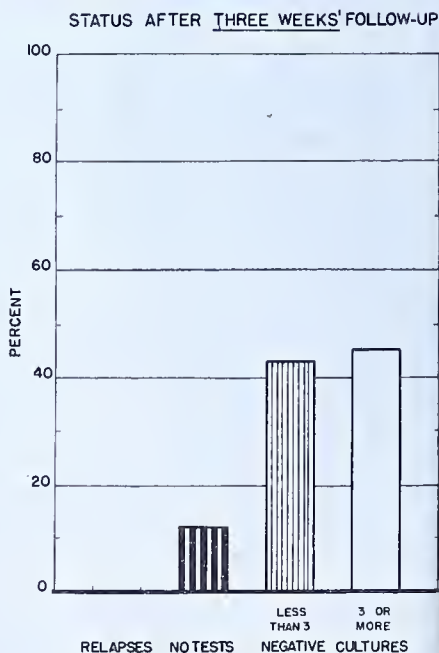
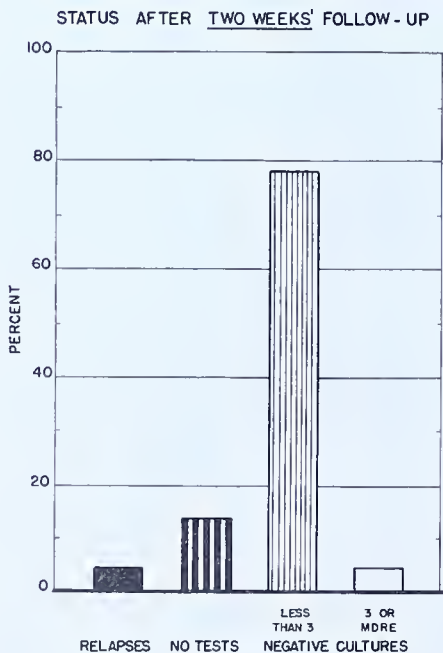
MONTHLY REPORT

DISAPPEARANCE OF SYMPTOMS BY END OF FOURTH WEEK OF OBSERVATION



SULFATHIAZOLE

LABORATORY FOLLOW-UP IN INDICATED PERIODS
ON PATIENTS SHOWING NO DISCHARGE AND CLEAR 2 GLASS TEST FOR 14 DAYS



NEW DRUGS

RAPID APPRAISAL REPORTS ARE PUBLISHED EACH MONTH ONLY FOR DRUGS IN GENERAL USE. RESULTS WITH NEW DRUGS INTRODUCED FOR CLINICAL EXPERIMENTATION ARE COMMUNICATED DIRECTLY TO THE RESEARCH CLINICS AND TO THE PHARMACEUTICAL LABORATORY MANUFACTURING THE DRUG. THIS INFORMATION IS AVAILABLE TO OTHERS UPON REQUEST.

Sulfathiazole Treatment of Gonococcal Infections in Men and Women. Results in 360 Patients

J. F. MAHONEY, Senior Surgeon,
C. J. VAN SLYKE, Passed Assistant Surgeon,
and

R. R. WOLCOTT, Passed Assistant Surgeon,
United States Public Health Service

A PREVIOUS report¹ has presented preliminary observations on sulfathiazole treatment of the gonococcal infections of 106 men. In order to establish a broader base on which a more mature evaluation of sulfathiazole therapy can be made, the therapeutic and toxic potentialities of this compound have been explored further. It is the purpose of this paper to record the complete results of sulfathiazole therapy in 285 men and 75 women infected with the gonococcus.

MATERIAL

The male patients comprised 230 admissions to the hospital and 55 admissions to the out-patient clinic; selection of cases was not exercised. Practically all of the male patients were in good general health with the obvious exception of the gonococcal infection.

The female patients were 75 prison inmates of the prostitute class. All but six had been sentenced for prostitution and all but three of the entire group readily admitted that they had been so occupied for periods ranging from 1 month to as long as 16 years.

With the exception of salpingitis accompanied by pain and fever in three instances, the female patients had few

symptoms attributable to the genital infection.

In order to afford a suitable observation period in each case, selection of female patients was exercised in one respect, namely, that only those inmates were included whose prison term was to be at least 100 days.

DIAGNOSIS

There was ample clinical evidence of a gonococcal infection in all male patients in this series, but a requisite for inclusion in this group demanded that cultures of the secretions yield gonococci. Note was also made of the stained-spread findings, the appearance of the two-glass urine test, the amount and character of the urethral discharge, and the presence and severity of complications of the disease.

In the case of women the diagnosis required clinical evidence of endocervicitis and positive cultures for gonococci from the urethral and/or cervical secretions.

ROUTINE PROCEDURES

The routine procedures were essentially the same for the hospitalized and the out-patient men since the ward patients were not confined to bed and were allowed moderate exercise. In addition to the diagnostic procedures outlined above, serologic tests for syphilis, complement fixation tests for gonorrhea, urinalyses, white blood cell counts, and hemoglobin determinations were conducted at the time of starting treatment

From the Venereal Disease Research Laboratory, U. S. Marine Hospital, Staten Island, New York.

¹ MAHONEY, J. F.; WOLCOTT, R. R.; VAN SLYKE, C. J.: Sulfamethylthiazole and sulfathiazole therapy of gonococcal infections. *Am. J. Syph., Gonorr. & Ven., Dis.* 24: 613-621, 1940.

and repeated during and at the conclusion of therapy. In some of the patients, serial determinations of the blood concentrations of free and conjugated sulfathiazole, as well as determinations of the alkaline reserve of the blood plasma, were made. Only in the hospitalized group was it possible to record temperatures four times daily. The patients on the ward were seen daily throughout the period of hospitalization, but the out-patients were usually seen only two or three times during the first week and once or twice each week thereafter. The out-patients were instructed not to void for at least 2 hours before presenting themselves for examination in order that reliable urethral spreads and two-glass urine tests could be made. Urethral spreads were prepared from the secretions of each hospitalized patient every morning before voiding the night urine into glasses for the two-glass test. Passage of urethral sounds and prostatic massages will be considered under "Criteria of Cure."

Women with uncomplicated gonococcal infections were not hospitalized but were given chemotherapy in the cell blocks. Such routine daily duties as janitorial or laundry work were continued by the inmates during the time they received treatment. Patients with acute gonococcal pelvic inflammatory disease were, of course, confined to hospital beds during the period of treatment. Routine urinalyses and blood studies were also conducted in the case of each of the female patients.

BACTERIOLOGIC METHODS

The Hucker modification of the Gram technic was employed in staining all spreads. Douglas chocolate agar and the Difco material for the growth of gonococci were the media used in all culture examinations. All cultures were incubated under 10 percent carbon dioxide tension at 35.5° C. for 48 hours. All questionable cases were confirmed by sugar fermentation tests. The microscopic and cultural investigations were in the hands of workers thoroughly experienced in this field.

DOSAGE

In the case of male patients, who were observed early in this series, and previously reported upon,¹ a variety of dosage schedules were employed in an attempt to ascertain the optimal amount of sulfathiazole which might effect a high cure rate with a minimum of toxic reactions. On the first day of chemotherapy the dose ranged from 2.0 gm. to 8.0 gm. and on subsequent days from 2.0 gm. to 4.0 gm. After preliminary experimentation the usual and recommended dosage, as shown in figure 1, was 2.0 gm. per day for a total of 10 days' medication. In no case was the drug continued longer than 12 days. All patients received the drug at 4-hour intervals during the day, i. e., at 8:00 A. M., 12:00 Noon, 4:00 P. M. and 8:00 P. M. The maximum total dosage administered to a male patient was 42 gm. in 10 days, and the minimum total dosage in a completed case was 8.0 gm. in 3 days.

The dosage of sulfathiazole was the same for all female patients, i. e., a total of 20.0 gm. in 10 days, given in 0.5 gm. doses at 8:00 A. M., 12:00 Noon, 4:00 P. M. and 8:00 P. M. A nurse supplied each patient with a single dose four times daily and observed her carefully to insure ingestion of the drug.

TOXIC MANIFESTATIONS

In spite of daily repeated and direct specific questioning which listed most of the common complaints ordinarily associated with sulfonamide therapy, 329 or more than 91 percent of the 360 patients, did not report any unpleasant symptoms which might have been attributed to the use of sulfathiazole. The remaining 31 patients, four of whom were definitely psychoneurotic individuals, reported one or more of the following symptoms: Headache, 16; vertigo, 9; weakness (general), 5; nausea, 2; insomnia, 2; rash, 2; malaise, 2; fever, 1; nervousness, 1; palpitation, 1.

The reactions listed above were usually mild and never more than moderate in character. There were no evidences suggesting the formation of renal calculi or

other serious untoward results of treatment.

The mildness and infrequency of the untoward symptoms recorded, and the fact that their presence was elicited through verbal listing of possible symptoms, cast some doubt on the assumption that sulfa-

thiazole was responsible. The possibility of coincidental occurrence must be considered.

BLOOD STUDIES

Hemoglobin determinations and white blood cell counts made before, during, and

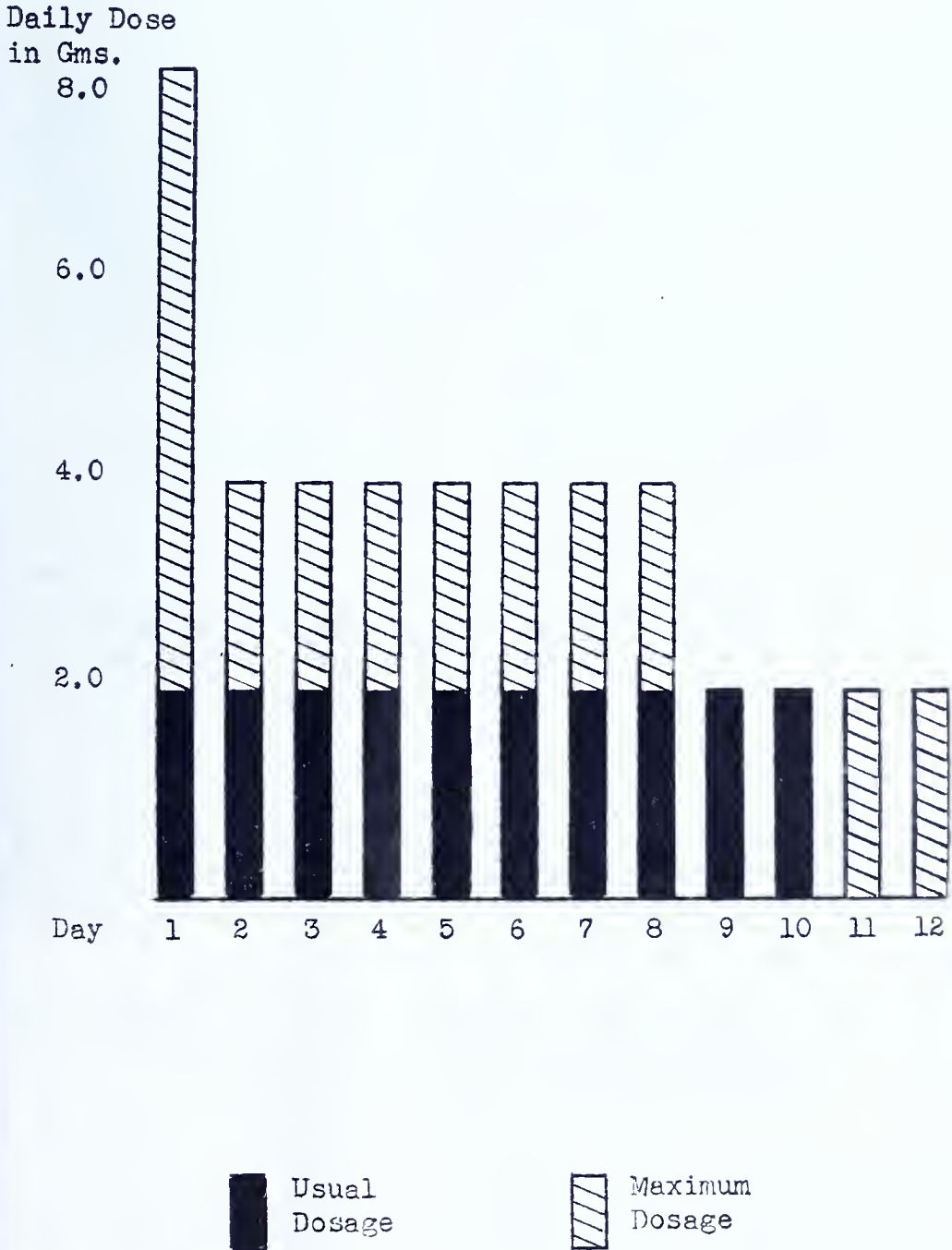


FIGURE 1.—Dosage schedule of sulfathiazole employed in the treatment of gonococcal infection in 285 men.

after sulfathiazole therapy did not reveal anemia or leukopenia attributable to therapy. In patients who had a leukocytosis before treatment, normal white counts were usually obtained within a few days of starting sulfathiazole therapy, if cure was effected. Differential cell counts in 75 patients did not reveal any remarkable changes.

Determinations of the carbon dioxide combining power of the blood plasma showed that the alkaline reserve of the blood remained within normal limits during and subsequent to treatment. In this connection it is well to note that sodium bicarbonate was not given.

Studies of the blood concentration levels of sulfathiazole were made in approximately 50 patients. It was found that the rate of absorption was not uniform in individuals of the same body weight who were receiving the same amount of the drug. Absorption, however, was usually complete in 4 or 5 hours. The degree of conjugation of the drug did not appear related either to the curative action or to the occurrence of toxic manifestations, nor did blood concentration levels of free sulfathiazole explain why certain patients responded to treatment while others failed.

CRITERIA OF CURE

Although a minimum time limit for the posttreatment observation of the patients was not established, many patients have been followed for periods of more than one year. The criteria of cure in all cases demanded complete subsidence of symptoms and clinical signs of gonorrhea, as well as repeated negative spread and culture findings.

In order to avoid a possible bacteriostatic effect of sulfathiazole in the secretions, no cultures were considered tests of cure unless the secretions were obtained at least 48 hours after the discontinuance of sulfathiazole therapy. The frequency with which positive cultures were obtained from failure cases during sulfathiazole therapy when blood concentration levels were relatively high indi-

cates that this precaution was based more on theoretical than on practical grounds.

Culture specimens were obtained from men by prostatic massage and urethral expression following the passage of a urethral sound. A minimum of three negative posttreatment cultures was demanded in each cured case.

The female patients were examined twice weekly during the posttreatment observation period which averaged 62 days. At each examination material for spread and culture studies was taken from the urethra and cervix. An average of 17 such examinations after treatment was made in each case. It is to be noted that a woman was not considered cured if any clinical evidence of gonococcal infection persisted, even though repeated spread and culture findings were negative.

RESULTS IN MEN

Although this portion of the report includes data on 285 men who received sulfathiazole for their gonococcal infections, it is possible to record the final results in only 213 male patients since 72 men lapsed treatment or observation before they had completed all of the tests of cure. Of the 213 completed cases, 177 (83.1 percent) satisfied all of the criteria of cure. If this group of 213 men is subdivided on the basis of previous sulfonamide therapy, it is found that 105 of 121 previously untreated patients (85.6 percent) were cured, while of those who failed to benefit by previous sulfonamide therapy 72 of 92 men (80.0 percent) responded satisfactorily to the administration of sulfathiazole.

Also, if a more accurate presentation of the efficacy of sulfathiazole in this group of 285 men is to be given, data on the 72 lapsed cases must be presented. Of this group of 72 patients who lapsed treatment or observation, 18 were lost at such an early period that a valid forecast of the eventual outcome could not be made. However, all these patients had had several consecutive negative urethral spreads and were clinically well when last observed.

The remaining 54 cases of the lapsed group had responded favorably and had been followed with negative cultures (an average of two per patient) but had not met the demands of one of the criteria of cure, namely, a minimum of three negative cultures *after* the period of medication. If the results of treatment of these 54 lapsed cases are added to the results obtained in the completed cases, the cure rates are altered slightly in the direction indicating greater efficacy of sulfathiazole. In the group previously but unsuccessfully treated with sulfonamides the percentage of cures from sulfathiazole therapy rises from 78.2 percent to 82.0 percent; in the previously untreated patients the cure rate advances from 86.7 percent to 89.7 percent, and the gross cure rate changes from 83.1 percent to 86.5 percent.

Among male patients there were 36 failure cases. Although sulfathiazole treatment usually caused a temporary clinical improvement, the failures were

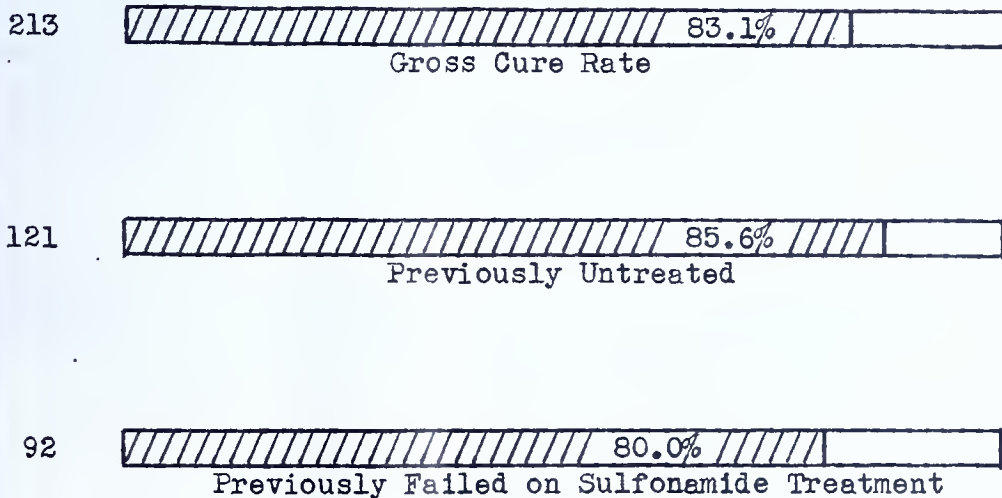
easily recognized clinically at once, or within a few days, after chemotherapy had been discontinued. Although culture studies were employed, this laboratory aid was not essential in the detection of the failures.

RESULTS IN COMPLICATED CASES

Complications were present in 23 of the 285 male patients. There were 12 instances of epididymitis, 8 of which responded favorably. In two cases relief of the epididymitis was secured without recession of the urethritis, while the remaining 2 patients failed to obtain more than temporary benefit from the therapy.

In 4 patients chronic arthritis antedated the urethral infection. No appreciable recession of the chronic arthritic condition was produced by sulfathiazole therapy, although the urethritis was rapidly and favorably affected in each instance.

No. of
Cases



(Criteria included 3 negative cultures after chemotherapy)

FIGURE 2.—Treatment of gonococcal infections with sulfathiazole—results in 213 men. (Criteria included 3 negative cultures after chemotherapy.)

Balanitis disappeared quickly in four instances, although the urethral infection was favorably affected in only three of the patients. One man with a periurethral gland abscess was successfully treated with sulfathiazole and had complete absorption of the abscess, while a second patient with a similar abscess did not respond to treatment.

An acute prostatic abscess underwent rapid and apparently complete absorption coincident with the cure of the urethritis. In another case, the abscess did not respond to therapy although the concomitant gonococcal urethritis was apparently cured. Subsequent to sulfathiazole therapy this abscess was opened surgically and the contents were cultured. Gonococci were not demonstrated. This case was classified as a failure.

RESULTS IN WOMEN

With one single exception 1,405 post-treatment culture studies, made in the 75 women, yielded negative results. In addition to the case giving a positive culture, five other cases were also considered failures on the basis of clinical findings alone. Thus, the cure rate established by sulfathiazole therapy of gonorrhea in 75 women was 92.0 percent.

In the case of women the cure rates cannot be made to show a comparison between previously treated and untreated patients. Although 28 patients of the series had received sulfonamide therapy (chiefly sulfapyridine) for gonococcal infections, such treatment had been given at least several months earlier for what was considered to be a separate and distinct invasion by the gonococcus. Since their last ingestion of any sulfonamide, all of these women had worked more or less regularly as prostitutes and so had had numerous opportunities to receive new infections.

Three episodes of acute salpingitis were seen in the group of 75 women. In two patients pain, fever, tenderness, and leukocytosis were present when sulfathiazole therapy was begun; in both instances all subjective symptoms of infection disappeared completely within 72 hours.

The third case of salpingitis occurred approximately 2 weeks after a 10-day period of sulfathiazole therapy. It developed in a patient who had already been classified as a failure because of a persistent mucopurulent cervical discharge although four culture studies had failed to reveal gonococci. A second course of chemotherapy effected a rapid subsidence of all signs and symptoms referable to the tubal involvement, as well as the cervical discharge which had persisted after the first course of sulfathiazole.

One instance of abscess of Skene's glands was seen in the series of 75 women. The abscess was exquisitely tender, approximately 2.5 cm. in diameter and at the initial examination exuded creamy purulent material. The tenderness and discharge disappeared slowly and were entirely gone within one week of the termination of chemotherapy. The swelling gradually decreased until it was only a small fibrotic thickening when the patient was last seen 90 days after the first examination.

Three women were pregnant at the time sulfathiazole therapy was begun. The duration of pregnancy was 2½, 3, and 4 months, respectively. Although these patients were not followed to term, sulfathiazole did not appear to alter the normal course of pregnancy, and each of them obtained clinical and bacteriologic cure of the gonococcal infection.

DISCUSSION

The findings in the present series point to several characteristics of sulfathiazole therapy which appear to possess advantages over other drugs of this type now available. An acceptable gross cure rate is attainable with a routine consisting of 2 gm. of the drug daily for a period not to exceed 10 days. On this basis the frequency and severity of toxic symptoms are reduced to a point where discontinuance of the drug is necessary only in patients displaying a true idiosyncrasy. Also, this level of medication reduces to a minimum the need for scrutiny of the blood and urine which is essential in safe

guarding the patient when large amounts of sulfonamide are administered.

Although the above results are based upon a single course of sulfathiazole treatment, it has been found that approximately three-fourths of the patients who fail to respond to the initial course are benefited by a second therapeutic attempt.

Previous studies of the use of *sulfanilamide* in the treatment of gonococcal infection disclosed the occurrence of persistent asymptomatic carrier states. In such patients, who were free from residual clinical evidence of illness, the causative organism could be demonstrated only by culture. This phenomenon has not been observed in patients treated with sulfathiazole although it is conceivable that an occasional instance of the kind may occur. The nonappearance of asymptomatic carrier states obviates much of the need for culture studies, adequate facilities for which are available only in the larger treatment centers. With a suitable period of posttreatment observation an accurate decision as to cure may be made on clinical evidence alone.

The prompt response to therapy observed in patients with severe complications of the disease, especially in women, gives rise to the belief that the frequency with which surgical interference has been required will be greatly reduced in the future. Complications were often favorably affected in patients who otherwise were not influenced by the treatment.

The cure rate attainable with sulfathiazole is apparently as high in acute gonococcal infections as in cases of longer duration. In this respect sulfathiazole is similar to sulfapyridine but distinctly superior to sulfanilamide.

There was no evidence which indicated that the duration of the obvious infection without treatment had any influence on the rate of cure. In other words, sulfathiazole therapy is just as effective if given early in the course of the infection as it is when treatment is deferred.

The therapeutic efficacy and the innocuous character of sulfathiazole in the dosage recommended renders it a promising agent for a broad-scale attack on the problem of gonococcal infections.

SUMMARY AND CONCLUSIONS

1. The results of sulfathiazole treatment of gonococcal infections in 285 men and 75 women have been reported.

2. The gross cure rate for the 360 patients was 85.4 percent.

3. A routine of 2.0 gm. of sulfathiazole per day for a period not to exceed 12 days was followed in the majority of patients.

4. No instance of severe toxicity was encountered, and mild toxic symptoms were observed only infrequently.

5. In the dosage mentioned the need of burdensome laboratory scrutiny of blood and urine during the period of therapy is reduced to a minimum.

6. Posttreatment asymptomatic carrier states were not observed. Patients who failed to respond to the therapy displayed clinical evidence of the disease.

7. Practically all of the 72 lapsed cases which are not included in the compilation of the cure rate were apparently cured at the time of the last observation.

8. Sulfathiazole therapy appears to possess the characteristics essential for an effective broad-scale attack upon the disease.

The Toxic Dose of Mapharsen Given in Interrupted Doses

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with the technical assistance of ANTHONY MUFF

IN A RECENT paper (1) we reported that the maximum tolerated dose of mapharsen (the hemi-alcoholate of meta-

amino-para-hydroxy phenyl-arsenoxide) administered to dogs by the continuous drip method was 10 milligrams per kilo-

gram of body weight per day for a period of 5 consecutive days. The minimum lethal dose under the same conditions was found to be 12 milligrams per kilogram per day. It was pointed out that while the total amount of mapharsen which may be safely administered by continuous drip was greater than that which might be given in a single dose, this amount might or might not be greater than could be administered during the same length of time by giving the drug in divided doses. The question raised was whether the drip method of administration increased the tolerance because of the rate at which the drug was given or whether the increased tolerance was simply a time effect. The experiments reported in this paper were made in an attempt to determine this point.

Every effort was made to keep the experimental conditions identical with those reported in the previous paper with the exception that the drip was omitted and the mapharsen was administered in three equal daily doses given at 6-hour intervals for each of 5 successive days.

Seventeen dogs were used, each weighing at least 10 kilograms. For at least 3 days prior to the beginning of the injections and during the experimental period the animals were fed a diet of dog biscuit which was high in carbohydrate and protein but low in fat. The animals were given liberal amounts of this food and of water during the 12-hour intervals in which they were not receiving arsenic. The mapharsen was dissolved in an appropriate amount of distilled water so that the calculated dose was contained in approximately 10 cubic centimeters of solution. The drug was injected rapidly into one of the leg veins. During this daily 12-hour interval in which the arsenic was given, the animals were kept quiet by the intravenous injection of sodium pentobarbital. At all times the anesthesia was maintained at the same level

that was necessary in our previous experiments with the continuous drip, i. e., the anesthesia was kept as light as possible so that during the greater portion of the time the animals were drowsy and would lie quietly but retained blinking eye reflexes.

TABLE 1

Dose of mapharsen (mg./kg./day)	Animals used (number)	Animals lived (number)	Animals died (number)
10-----	5	4	1
12-----	5	3	2
14-----	4	0	4
16-----	2	1	1
18-----	1	0	1

Ten cubic centimeters of blood was taken for an arsenic determination each morning before the first dose of mapharsen and each evening just before the last dose was administered. All urine and feces were saved for arsenic determinations. Animals which survived the treatment were sacrificed at varying intervals thereafter. Under full sodium pentobarbital anesthesia they were exsanguinated by severing the abdominal aorta. Tissue specimens were taken in duplicate for arsenic determinations whenever the amount of tissue would permit. All arsenic determinations were done by the method of Chaney and Magnuson (2).

RESULTS

The mortality by groups which are designated by the amount of mapharsen administered per kilogram of body weight per day is indicated in table 1. Unless the animal died before the treatment period was concluded he thus received five times this amount as the total dose.

Table 1 shows that the maximum tolerated dose is 10 milligrams per kilogram of body weight per day for a 5-day treatment period, and that the minimum lethal dose under the same conditions is 14 milligrams per kilogram per day.

The condition of the animals during the period in which treatment was given was very similar to that encountered in the experiments in which the drug was given by continuous drip with the excep-

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tion that there was more vomiting by those that received the interrupted doses. Hematuria was again encountered in some animals. As with the previous groups there were no late deaths following treatment; the animals that died did so either during or immediately following the treatment. Within 2 or 3 days after the administration of arsenic had been stopped the animals appeared to be normal except for the one dog which lived after taking 16 milligrams per kilogram per day. This dog was very lethargic, refusing to walk and to eat for nearly a week following treatment. At post mortem examination 44 days later, no gross abnormalities were noted, though significant amounts of arsenic were still found in some tissues.

In the previous group of animals to which the arsenic was given by the drip method, it was noted that there was a direct relation between the amount of arsenic retained and the fate of the animal. This relationship was not so clear in the present group to which the drug

was given in interrupted doses. The total urinary and fecal excretions were determined and the arsenic which was not excreted through these channels was assumed to be retained, though such an assumption introduces some error due to the lag in fecal excretion. Based on the number of stools per day, the lag was about equal in the two groups. The percentage retained was multiplied by the amount of mapharsen given in milligrams per kilogram per day to obtain the amount retained in milligrams per kilogram per day. This was done for the total excretion for the 5-day period as well as for the first 2 days only. The results were arranged in order of the amount retained and are indicated in table 2. When the animal died the number of days during which treatment was given before death occurred is indicated by the number following the word "died." Two animals which lived are not included because losses occurred in the collection of urine specimens.

TABLE 2

Total excretion 5 days				Excretion first 2 days only			
Mapharsen given (mg./kg./day)	Dog number	Mapharsen retained (mg./kg./day)	Fate of dog	Mapharsen given (mg./kg./day)	Dog number	Mapharsen retained (mg./kg./day)	Fate of dog
10.....	50	5.5	Lived.	10.....	50	5.8	Lived.
10.....	49	6.7	Lived.	10.....	49	7.6	Lived.
10.....	51	7.3	Lived.	10.....	48	8.0	Died (2).
12.....	45	7.9	Lived.	10.....	51	8.4	Lived.
12.....	44	8.0	Died (3).	12.....	44	8.8	Died (3).
10.....	48	8.1	Died (2).	14.....	52	9.1	Died (4).
12.....	36	8.4	Lived.	12.....	36	9.3	Lived.
14.....	52	9.3	Died (5).	12.....	45	9.3	Lived.
12.....	47	9.4	Died (2).	12.....	47	9.4	Died (2).
16.....	40	9.8	Lived.	18.....	38	10.9	Died (4).
18.....	38	10.4	Died (4).	14.....	42	12.0	Died (2).
16.....	41	11.1	Died (4).	16.....	40	12.2	Lived.
14.....	42	12.0	Died (2).	16.....	41	12.2	Died (4).
14.....	46	12.8	Died (1).	14.....	46	12.8	Died (1).
14.....	39	13.3	Died (1).	14.....	39	13.3	Died (1).

It may be seen that these figures do not present the sharp differentiation between those animals that lived and those that died, such as was encountered in those that received continuous drip. Furthermore, the total excretion was almost always less than that found in the previous group. The average total excretion dropped from 42.2 percent in the first

group to 28.4 percent in the present group. This difference was most marked in the urinary excretion which averaged 35.6 percent of the arsenic administered with the continuous drip, but only 16 percent of that given by interrupted doses. The most probable explanation for this appears to be in the difference in the fluid intake. With the continuous drip the ani-

imals were receiving approximately 600 cc. of intravenous fluid each day and in addition were drinking water as desired. With the interrupted doses the fluid intake was dependent upon the thirst of the animals, which was very irregular, many of the animals being nauseated and refusing to drink.

It is difficult to explain why these animals tolerated as much mapharsen as those that received the drug by the drip method even though they excreted less arsenic. Since the primary cause of death in each group seems to have been a diffuse capillary damage one wonders whether the prolonged addition of mapharsen to the blood stream may have been in part responsible.

The amounts of arsenic found in whole blood at the various time intervals and with various dosage levels are indicated in figure 1. The ordinate represents micrograms of arsenic per 100 cubic centimeters of whole blood. Along the abscissa the days of treatment are indicated. The numerals mark the start of

each day and the marks between the numerals indicate the end of each day. Since the blood specimens were taken just prior to the administration of mapharsen the arsenic levels represent minimum values. When samples were taken in the morning the animals had received no arsenic for 12 hours, and when taken in the evening they had received no arsenic for 6 hours.

In the group that received 10 milligrams per kilogram of body weight per day only one animal died, number 48. The peak value represents blood taken post mortem 2 hours after the administration of mapharsen. In the group that received 12 milligrams per kilogram of body weight per day, two animals, numbers 47 and 44, died. The peak value of dog 44 is from blood taken post mortem and 1 hour and 15 minutes after the last dose of mapharsen had been given. In the 14- to 18-milligram group all of the animals died except number 40, which was extremely ill for a week following treatment. None of the blood specimens are post mortem samples.

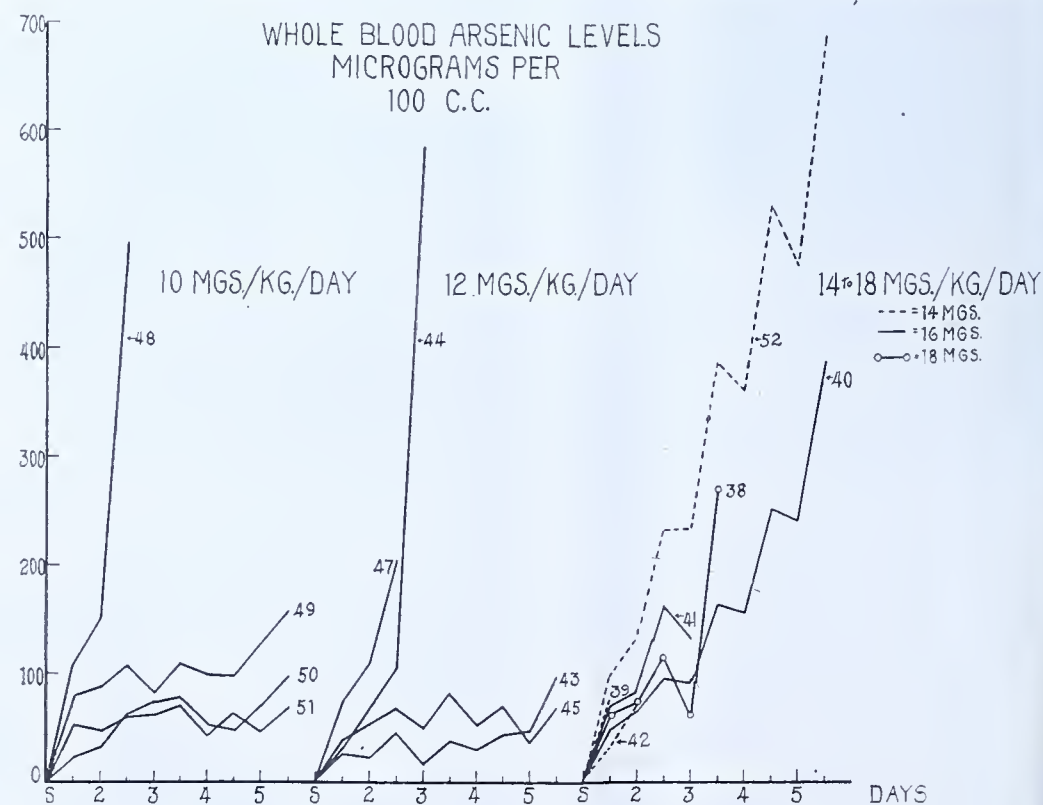


FIGURE 1.

As in the animals treated by the drip method there appears to be no definite blood arsenic level at which death occurs, but for those animals that died the curve representing the concentration of arsenic in the blood was somewhat steeper.

The results of the arsenic determinations on tissues obtained on death or sacrifice of the animals are recorded in table 3. The results are expressed as micrograms of arsenic per 100 grams of wet tissue with the exception of the figure for bile which represents the total amount of arsenic found in the gall bladder at the time of autopsy. The number following the word "died" in the fate column indicates the day on which the animal died.

The results of these analyses need no comment other than to point out that once again there is a tendency for a somewhat

longer retention of arsenic than was encountered in animals given small doses by the continuous drip method (3). The animal that received 16 milligrams per kilogram per day and survived had significant quantities of arsenic in the liver, kidney, bone, and spleen 44 days after cessation of treatment.

COMMENT

It appears from the results of these experiments that the continuous drip method of administration of mapharsen increases the tolerance to the drug not because of the particular method of administration but rather because the dose is spread out over a 5-day period. The assumption by Baehr, Leifer, Chargin and Hyman (4) that some of the toxic reactions from arsenicals, particularly nitritoid, may be the result of a speed shock

TABLE 3

Dose	10 mg./kg./day					12 mg./kg./day				
	48	35	49	50	51	47	44	43	45	36
Dog No.....										
Fate.....	Died (2)	Lived	Lived	Lived	Lived	Died (2)	Died (3)	Lived	Lived	Lived
Days after treatment.....	7	10	17	17	17			25	30	67
Heart.....	190	17	0	0	28	144	256	10	10	0
Lungs.....	736	23	5	5	10	450	800	5	5	0
Bile.....	380		0.5	0	0	450	110	0.7	0	0
Liver.....	2,050	116	44	19	17	575	1,610	19	20	5
Pancreas.....	316	26	5	5	15	237	417	16	5	10
Kidney.....	1,400	188	54	60	40	700	1,240	29	13	10
Testicles.....	80	11	0	0	5	79	135		0	0
Skeletal muscle.....	186	32	0	12	8	145	154	10	5	5
Aorta.....	299	34	39	28	80	622	448	0	0	
Peripheral nerve.....	171		223	73	0	68	121	0	0	0
Thyroid.....	262		405	107	38	183	244	0	0	0
Brain.....	34	22	5	15	20	25	29	10	0	0
Femur.....	131	82	0	10	0	61	60	40	0	0
Spleen.....	722	160	55	63	32	340	350	24	10	12

Dose	14 mg./kg./day				16 mg.		18 mg.
	46	39	42	52	41	40	38
Dog No.....							
Fate.....	Died (1)	Died (1)	Died (2)	Died (5)	Died (4)	44	Died (3)
Days after treatment.....							
Heart.....	125	120	133	440	341	0	300
Lungs.....	190	310	500	770	900	0	660
Bile.....	445	2,600	1,400			0	420
Liver.....	715	2,200	1,900	2,045	2,350	47	1,920
Pancreas.....	146	242	150	530	615	0	630
Kidney.....	1,010	800	1,212	1,730	1,770	90	1,360
Testicles.....	112			210	225	0	160
Skeletal muscle.....	156	150	170	332	315	0	315
Aorta.....	246	194	199	552	483	0	448
Peripheral nerve.....	86	167	24	380	255	0	227
Thyroid.....	250	120	92	724	367	0	418
Brain.....	30	17	15	70	54	0	63
Femur.....	83	25	68	200	227	90	75
Spleen.....	295	440	325	1,700	845	165	730

is all well and good, but the late toxic reactions due to arsenic poisoning are another matter. Arsenic is a cumulative poison which acts relatively slowly, and it evidently makes no difference whether the drug is given slowly and continuously over a 12-hour period or in three single large doses during the same time-interval. The net effect is the same in either case.

It may be said that a possible advantage of the drip administration is that theoretically higher concentrations of mapharsen are maintained in the blood stream for a longer time-period than when the drug is given in interrupted doses, but in our experience the amounts of arsenic found in the blood are not significantly different. It may be, of course, that following interrupted doses, a large portion of the arsenic is rapidly rendered therapeutically inactive and that a large portion of the arsenic found is of no therapeutic value, while with the drip method arsenic of known therapeutic value is constantly being added to the blood stream. Such assumptions are purely speculative and cannot be decided on an experimental basis at present.

If the tolerance to arsenicals is not truly increased by the drip method of administration one is justified in asking whether or not the ultimate fate of the continuous drip may not be the same as that of the various intensive interrupted-dose plans of treatment such as were the vogue a few years ago and which showed such poor ultimate results in the Cooperative Clinical Group surveys. Time alone will give the answer. Meanwhile, experimental

The mapharsen used in this study was supplied by Parke, Davis & Co.

evidence appears to indicate the need for great caution in the use of the continuous drip method of treatment.

CONCLUSIONS

1. The maximum tolerated dose of mapharsen given to anesthetized dogs in three daily doses for each of 5 successive days was found to be 10 milligrams per kilogram of body weight per day.

2. The minimum lethal dose of mapharsen administered under the same conditions was 14 milligrams per kilogram per day.

3. The maximum tolerated dose and minimum lethal dose do not differ significantly from those found by continuous-drip administration under identical conditions.

4. The increased tolerance to mapharsen when given by the continuous drip is the result of spreading the total dose out over a 5-day period and not due to the drip method of administration.

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Program of Division of Social Protection Federal Security Agency

ELIOT NESS

Director, Division of Social Protection

IT IS THE purpose of the Federal Defense Program to safeguard the health and morale of the armed forces and of

the workers in defense industry. The Division of Social Protection has been formed to implement this purpose.

The first task of this Division is to promote the public health by the reduction of venereal disease through the repression of commercialized prostitution.

The responsibility of the Division of Social Protection is by no means limited to this task, however.

The Division is concerned with the protection of the community, and particularly of its girls and young women, from prostitution and other related social hazards. It also stimulates the constructive treatment and care of girls and women detained by the police.

In its long term aspects, this Division is an integral part of the total public welfare program. It depends for its effectiveness upon the established agencies for public health, medical care, law enforcement, public assistance, recreation, and child protection, and in turn supplements these agencies in its particular field.

The program of the Division of Social Protection is summarized below under four headings, relating to repression, treatment, protection, and cooperation.

A. *Repression of Commercialized Prostitution.*

1. The method adopted by the Division towards the control of venereal disease in the repression of commercialized prostitution for the purpose of reducing to a minimum contacts by prostitutes with men in the armed forces and in defense industry.
2. While those interested in the program believe in its moral implications, the Division considers it most important that the program be administered as a public health and protective measure without any suggestion of a moral crusade. One reason for this is the almost universal resistance of the citizenship of this country against governmental supervision of sexual morality. It may be that this resistance is allied to the fundamental American concept of religious liberty, since religion and morals are so closely associated. Just as the good citizen who is convinced of the importance of religion in human life may be strenuously

opposed to any attempt by government to guide the practice of religion, so the good citizen while believing strongly that extramarital relations tend to destroy the values of family life may still be unwilling to see the Federal Government attempt to control such relations.

3. The program is unalterably opposed to any toleration of commercialized prostitution, either in segregated districts or under medical supervision. This is based upon experience and studies which have proven that segregation does not segregate and that medical supervision alone cannot prevent the spread of venereal disease.
4. It is the policy of this Division to work through State and local authorities. It is the hope of those responsible for the administration of this program that the repression of commercialized prostitution will continue as a permanent policy throughout this Nation after this emergency is over. This can be accomplished only when State and local authorities and local communities are convinced that repression rather than toleration is the answer to the problem. It is, therefore, the responsibility of this Division to attempt to bring about the voluntary adoption of its program by local authorities as a permanent policy. The establishment by military authorities of areas as out of bounds for men in uniform, or the invocation of the May Act, are measures to be taken only as a last resort. Experience in the last war, and the attitude of Federal and local authorities to date in this emergency, all point to the likelihood that our program can be established in most defense areas on a voluntary basis.

B. *Treatment of Prostitutes.*

1. The aim of this program is to get local authorities to deal with the individual prostitute as a human being with the aim that those who are capable of rehabilitation can be

helped back to ways of life which are more constructive.

2. Our field representatives will seek the establishment of facilities for the classification of girls and women picked up by the police so that those who can be helped can be separated from those who show little hope of rehabilitation, and those in need of special treatment can be given such treatment or sent to places where treatment is available.
3. Our field staff will seek provision of adequate facilities when needed for the treatment of women, on an individualized basis, whether that treatment be (a) medical, (b) custodial, (c) training, (d) placement in jobs, (e) placement in family foster homes, (f) assistance to return to their own homes, or (g) other constructive measures.

C. The Protection of Girls in Defense Areas.

1. Protection of girls in defense areas involves supervision of places of employment where (a) wages may be inadequate to meet the girls' minimum requirements for food and shelter and (b) where the girl employee may be subject to pressure to engage in prostitution as a consequence of her employment.
2. It likewise involves supervision of places of commercial recreation where girls may be in danger of being led into prostitution.

D. Cooperation with other Agencies.

Those engaged in this program are well aware that this Division is only one of many agencies whose work is necessary to bring about the desired results.

1. We do not attempt to work with the man in uniform, leaving his education with reference to social hygiene and the control of his actions to the military and naval authorities.
2. We are fully convinced of the importance of such positive action as the provision for recreation and other leisure time activities for the soldier and sailor, but leave that to the military and naval authorities as sup-

plemented by the Division of Recreation of this Agency, by the United Service Organizations, and by many other interested agencies and organizations.

3. We are vitally concerned that those persons with venereal disease receive prompt, effective, and conclusive treatment so that, first, they may be made noninfectious and, second, cured, and we know that the U. S. Public Health Service is on that job.
4. In the field of law enforcement we depend on local authorities, the Military Police, and in the exceptional case on the Department of Justice.
5. In the care of the apprehended prostitute and in the protection of girls and young women in danger of prostitution, we depend upon the facilities and resources of the agencies of local, State and Federal Governments.

CONCLUSION

The Division of Social Protection then, takes its place as an integral part of the Office of Defense Health and Welfare Services. On the State and local level it will maintain its responsibilities in a cooperative and constructive fashion working with public officials, private agencies, and interested citizens. It stands ready to modify its efforts and plans in accordance with new experiences and developing community needs. It is the will and desire of the American people to protect the health and morale of the men in its armed forces and defense industries. The Division of Social Protection will contribute to this end. We intend so to plan and execute the program that it will be accepted by the States and become the permanent policy of local government throughout the nation.

DIAGNOSIS

Serodiagnostic tests for syphilis in State laboratories. The 1941 evaluation of their performance. Thomas Parran, H. H. Hazen, J. F. Mahoney, Arthur H.

Sanford, F. E. Seneear, Walter M. Simpson, and R. A. Vonderlehr. J. A. M. A., Chicago, 117: 1167-1168, Oct. 4, 1941.

In the publication of their reports for the previous 6 years' study, the Committee on Evaluation of Serodiagnostic Tests for Syphilis has hidden the identity of the participating laboratories by the use of code designations. In the present report no such designations are used in order that the medical man may judge the efficiency of the test performances in the laboratory to which his specimens are sent.

For this 1941 survey identical whole blood specimens collected from 230 syphilitic donors and from 132 presumably nonsyphilitic donors were sent to each participant. Similar specimens were tested in the control laboratories of Eagle, Hinton, Kahn, Kline, and Kolmer. The Venereal Disease Research Laboratory of the Public Health Service served as referee in the matter of suitability of each donor for the purpose of the study. A satisfactory performance was arbitrarily considered to be one which attained a sensitivity rating not more than 10 percentage points below that of the suitable control. In specificity a rating below 99 percent was considered unsatisfactory. Doubtful reactions were accorded a one-half credit if occurring in the serum of a syphilitic donor and a one-half demerit if in the serum of a nonsyphilitic donor.

The comparative results of this study are shown by four charts. Chart 1 portrays the results obtained in the 1941 survey by 32 State laboratories utilizing the Kahn standard procedure. The control performance is that of Dr. Reuben L. Kahn. Chart 2 shows the ratings of 32 State laboratories which used complement fixation procedures. The control performances are those of Drs. Harry Eagle and John A. Kolmer. Chart 3 is an array of the results of 16 laboratories utilizing the Kline slide technic, and Chart 4 is a similar presentation of the laboratories which carry out the Hinton and Eagle flocculation methods.

It is possible that the degree of uniformity between the majority of State laboratories and their respective control may represent the upper limit attainable within the technical methods which are now available. If this is true, the efforts of the future may well be directed toward the maintenance of the present standards and toward the adoption of such sound advances as many be developed in the basic science. Since from one-half to one-fourth of the volume of serodiagnostic work is done outside the State laboratories, any comprehensive plan for the general improvement of methods must include the smaller laboratory units. Many States are placing in operation an arrangement by which the State laboratory will serve as an evaluating, consultative, and training center for the smaller units. Such a plan should have the ultimate effect of assuring an acceptable standard of serologic results within the limitations of methods in general use at the present time.

The development of general paresis following essentially normal spinal fluid findings. Report of a case. Israel Kopp and Harry C. Solomon. Am. J. Syph., Gonor. & Ven. Dis., St. Louis, 25: 583-590, Sept. 1941.

The authors present the case report and tabulate the clinical, serologic, and therapeutic course of a male patient with early minimal spinal fluid involvement, from the onset of a syphilitic infection to the development of general paresis.

In 1925, when the patient was 22 years of age, he had a primary syphilitic lesion followed by secondary skin manifestations. He was given 14 intravenous arsenical and 25 intramuscular mercury injections over a 9½ months' period. His blood Wassermann reaction became negative. A spinal fluid examination (14 months after the primary lesion) was normal, except for the important finding of a white cell count of 22, indicating a meningeal reaction. Because of a moderately positive Wassermann blood test 3 months later, additional chemotherapy was given. A second spinal fluid exami-

nation was made in 1928, 3 years after the primary lesion and following 33 months of treatment which had consisted of 34 intravenous injections of an arsphenamine preparation, 25 intramuscular injections of mercury, and 25 intramuscular injections of bismuth. The spinal fluid was negative except for a very slight trace of albumin and a gold sol curve of 1222210000. The changes in the spinal fluid were attributed by the attending physician to the presence of contaminating blood. It was decided that since the patient's blood Wassermann and spinal fluid serologic tests were negative, sufficient antisyphilitic treatment had been given. A 6 months' probationary period was advised, but treatment was nevertheless continued for 14 months to March 1929. During this time, the Hinton reaction of the blood was negative on nine occasions.

In January 1930, after 10 months without treatment, the Hinton blood test was again found positive, and further antisyphilitic treatment was given. Because of repeated fluctuations of the blood tests, treatment was administered for an additional 9 years by various physicians and clinics. The significance of the serologic relapse of the blood was overlooked. O'Leary and coworkers (*Arch. Dermat. & Syph.*, 35: 387, 1937) have said that a relapse of the Wassermann reaction of the blood from negative to positive in cases of early or late syphilis in which asymptomatic neurosyphilis was demonstrated calls for another test of the spinal fluid. However, in this case, the test of the spinal fluid was not repeated until 1940.

For 2½ years before the patient was admitted to the Boston Psychopathic Hospital in January 1940, he had been "nervous", tired easily, and worried considerably. For the last 2 months of that period his behavior had been bizarre. He insulted his customers, swore excessively and profanely, disregarded traffic signals, threatened and abused members of his family, and used very poor business judgment.

At the time of admission, his pupils were equal in size and reacted normally.

No abnormal reflexes were found. The mental examination showed a variable mood, impaired memory, poor grasp of general information, poor judgment, and no insight. A Hinton blood test was positive. The spinal fluid examination showed the following: Wassermann reaction positive in 0.1 cc.; 3 lymphocytes and 1 polymorphonuclear cell; total protein, 64 mg. percent; globulin, two plus; sugar, 63 mg. percent; gold sol, 5554321000.

A diagnosis of general paresis was made. Artificial fever followed by malaria and tryparsamide were administered with improvement in the patient's mental condition. After 6 months in the hospital, the patient was allowed to go home.

The authors review the literature on the subject of parenchymatous neurosyphilis developing after essentially normal spinal fluid findings. They found only one report of a case in which tabes dorsalis or general paresis developed following the previous finding of a negative spinal fluid test. Meyerbach (*Ztsch. f. d. ges. Neurol. u. Psychiat.*, 67: 245, 1921) observed a patient whose spinal fluid was negative 3 years after his syphilitic infection, but who had general paresis with typical serologic findings 5 years later.

The authors present this case history as a reminder that there are exceptions to all rules, and to emphasize that clinical judgment is always demanded in the treatment of syphilis.

Infectious relapse in syphilis. J. C. Kern. *Northwest. Med.*, Seattle, 40: 328-332, Sept. 1941.

The frequency of relapse cannot be determined with accuracy since lack of cooperation and relapse are closely associated and, because of their comparative insignificance, mucocutaneous relapse lesions pass unnoticed more frequently than not. All of the 80 cases selected for this study were observed in the stage of relapse at Vanderbilt University Hospital Clinic. The preponderance of white patients in this group (70 percent) in a clientele where the ratio of white to Negro patients is 1:2, is probably due to

the low index of suspicion and the phlegmatic attitude of the southern Negro.

After his careful analysis of these 80 cases, Kern reaches the following conclusions: Relapse occurs most frequently in patients whose treatment is begun in the primary stage of infection, slightly less frequently when treatment is begun in the secondary stage, and extremely infrequently when it is begun in the latent stage. Two-thirds of the patients developing mucocutaneous relapse have lesions at sites which are particularly favorable for transmission of infection. Relapse is characterized by paucity of lesions. These are usually papular or annular in type. Serologic tests for syphilis are positive in practically 100 percent of relapse cases. Eighty percent of recurrent lesions develop in the first 2 years of infection, if treatment is suboptimal; if the treatment is optimal relapse may be delayed longer. In two-thirds of the cases of relapse it occurs within 1 year after treatment ceases. As a rule the frequency of relapse decreases as the number of arsenical injections increases. Irregularity of treatment does not seem to be an important factor in relapse, when treatment is definitely inadequate, but irregularity may be blamed for 75 percent of infectious relapses that occur after 20 or more arsenical injections. The accepted standard of adequate treatment will not prevent infectious relapse in all cases.

TREATMENT

Observations on untreated patients with gonococcal infection and those receiving chemotherapy. Alfred Cohn, Boris A. Kornblith, and Arthur Steer. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 557-565, Sept. 1941.

The patients included in this study were divided into four groups: (1) An untreated group of 29 cases; (2) those treated with sulfanilamide, 97 cases; (3) those treated with sulfanilyl-sulfanil-

amide, 39 cases; (4) those treated with sulfapyridine, 47 cases. In addition, observations were made on patients who were resistant to one drug, and in whom the same drug was repeated or a new one substituted. All patients were ambulatory.

The criteria for diagnosis and cure included repeated smears and cultures for gonococci, provocative tests, the complement fixation test, and an adequate clinical, bacteriologic, and serologic follow-up for an average of 5 months.

Cultures were found to be far superior to the stained-smear method for diagnosis of gonococcal infections.

Of 29 patients who received no treatment whatever, 5 were cured spontaneously. The number of complications occurring among these untreated patients was higher than among patients receiving chemotherapy. Fifty percent of the patients treated with sulfanilamide and the same percentage of patients treated with sulfanilyl-sulfanilamide were cured. The results with the above two drugs were somewhat better when they were not given until 3 weeks after onset of the infection.

With sulfapyridine treatment, 89.4 percent of the patients were cured. This treatment was effective regardless of the duration of the disease.

Repeated courses of the same drug when the initial course was unsuccessful failed to produce cures in most cases. It is suggested that sulfapyridine be tried if sulfanilamide or sulfanilyl-sulfanilamide proves unsuccessful.

Observations on untreated patients and on those resistant to all chemotherapy suggest the possible development of a natural defense mechanism which may be sufficiently effective to overcome the gonococcal infection.

Test tube experiments have shown a direct bactericidal action on gonococci of the sulfonamide compounds used here. Sulfanilamide and sulfapyridine showed a smaller bactericidal effect than sulfanilyl-sulfanilamide. In animal experiments the protective power of sulfanilyl-sulfanilamide and of sulfapyridine was

10 times stronger than that of sulfanilamide, when tested in mice which had been experimentally infected with gonococci. It is evident that the mode of action of these chemotherapeutic agents differs in test tube experiments, in animal experiments, and in man. Perhaps, in the naturally susceptible host, man, a defense mechanism influences the action of these drugs.

Short term intensive arsenotherapy of early syphilis. Preliminary report. Arthur Schoch and L. J. Alexander. *Am. J. Syph., Gonorr. & Ven. Dis., St. Louis*, 25: 607-609, Sept. 1941.

The authors state that some modification of the 5-day treatment for syphilis is highly desirable, if not imperative. A modification in which hospitalization of patients is not necessary seems the most practical.

In July 1940, Alexander began treatment with mapharsen of a patient with seropositive primary syphilis. This patient was given 20 injections of mapharsen in full therapeutic dosage over a period of 28 days. Eight patients were so treated later, each with some slight break in continuity, but each received 20 doses in 30 days. The complete absence of serious treatment reactions in this first group of patients stimulated the authors to modify the procedure. The modification consisted of giving two 0.06 gm. doses of mapharsen $\frac{1}{2}$ hour apart each day for 10 days, the injections being given rapidly by syringe method, each dose dissolved in 10 cc. of sterile distilled water. Twenty-nine patients who had primary or secondary syphilis on admission were treated by one or the other of the above-mentioned procedures.

Serologic tests of the blood serum were made at frequent intervals, using the Kolmer complement fixation reaction, the standard Kahn, and the standard Kline flocculation tests. The Kolmer and Kline tests were done quantitatively, using normal saline as a diluent.

Of the 29 patients who have thus far completed this system of treatment, 5 were women (2 Negroes and 3 white

women), and 24 were men (10 Negroes and 14 white men). Three patients were in the seronegative primary stage when treatment was begun; when it ended, 10 were in the seropositive primary stage, and 16 were in the secondary stage of the disease.

After institution of treatment, a temporary rise in the reagin titer was noted in six of the patients. One of these was seronegative the first 2 days of treatment and then had a transient but definite seropositivity for 14 days.

A definite and steady decline in the reagin content, as measured quantitatively by both complement fixation and flocculation tests, took place to the point of complete disappearance in an average of about 10 weeks from the beginning of treatment in 11 patients. Involution of primary lesions and lesions in secondary eruptions took place at about the same speed as that observed under orthodox treatment.

One patient had a reinfection from a known source (a patient with secondary syphilis) under the observation of the authors. The second chancre was dark-field positive and was allowed to progress from the seronegative to the seropositive stage before treatment was reinstituted. One other patient had what must be considered a relapse, although the authors have strong reason to believe it might be a reinfection.

In an addendum, the authors state that 7 months' further observation discloses the fact that 26 patients are clinically and serologically well. This number includes the patient who had the clinical relapse and the one with the reinfection, both of whom were re-treated. Two patients had a serologic relapse. These two had the only positive spinal fluid Wassermann reactions in the series. One patient has a positive Kline test only.

Although the series is small and this is a preliminary report only, the authors are impressed by the comparative absence of treatment reactions. No serious reactions occurred, and only 11 patients complained of transient nausea and vomiting after the second, third, or sub-

sequent injections. Twenty-three of the 29 patients had Herxheimer reactions. In none of the patients was treatment discontinued because of treatment reactions. One patient had a scarlatiniform skin eruption on the last day of treatment. No cases of jaundice, encephalitis, or severe dermatitis were encountered in this small group.

The use of the B. L. B. oxygen inhalator as an adjunct to hyperpyrexia. Harry C. Knight. *Hosp. News* (processed), U. S. Public Health Service, Washington, 8: 13-15, Aug. 15, 1941.

The oxygen inhalation apparatus devised by Boothby, Lovelace, and Bulbulian, because of its simplicity and high degree of efficiency, has proved a most satisfactory means of administering oxygen to patients receiving treatment in a hypertherm. The nasal type of mask is preferable for such use. Cyanosis is rapidly relieved in all cases, with obvious improvement of the patient's general condition. Dyspnea is usually relieved and air hunger always alleviated. The claustrophobia which is often a psychic side-effect of air hunger is frequently mitigated. Falling blood pressure, that danger signal of a weakening circulatory system, is benefited greatly owing to the decreased load on the heart. The oxygen inhalations give many patients an increased feeling of well-being which reduces restlessness; the shallow respirations induced by the use of narcotics seem to become deeper and the respiratory exchange more efficient. Nausea, while it is not a common complication, is considerably benefited.

Oxygen inhalations are not a panacea for complications which occur during hyperpyrexia. They do not supplant constant, careful observation of the patient by trained personnel, nor the intelligent and timely use of the various sedatives and stimulants which have long been in use. They do provide an addition to the equipment of the treatment room by adding to the safety and comfort of the patient to a very high degree. By their use many patients are enabled to receive

treatment who otherwise would not have been able to complete a single treatment. Upon the patient's return to his bed the supplemental use of the inhalator is especially valuable in combating delayed blood pressure drop.

The treatment of the peripatetic patient. Editorial. (J. E. M.). *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, 25: 643-644, Sept. 1941.

Some persons, such as traveling salesmen and actors, spend most of their time in transient living. Should such a person acquire syphilis, he usually has considerable difficulty in receiving proper treatment for it. Forced to consult a series of physicians, he is subjected to changes in type or manner of treatment, to varying degrees of expertness in its administration, and to differences of opinion, sometimes legitimate and other times due to ignorance, as to what should be done. Only too often these differences of opinion are laid before the patient, with the result that the patient is hopelessly confused as to his proper course, and often so discouraged by the seeming lack of agreement between physicians that he abandons further treatment.

The writer suggests the following solution for this problem: The physician who inaugurates treatment should provide the patient with a series of documents, including (1) a copy of his history and the record of his physical examination, to spare him the necessity of repeating this in detail to each new physician; (2) a written outline of treatment, planned as definitely as possible with dates, drugs, and dosage for several months in advance and to be followed, barring unforeseen complications, by each of the physicians who sees the patient; (3) the name and address of a physician in each town (secured from the American Medical Association Directory) on the patient's itinerary, together with a blanket letter of introduction. This letter should specify the fee which the patient is able to pay for various treatment procedures.

This system retains the management and direction of the patient's treatment,

and the responsibility for the ultimate outcome, in the hands of a single physician. It is assumed that the directing physician is competent to direct and carry out antisyphilitic treatment. Even if he is not, it is often true that bad advice from a single source is better than conflicting good advice from many sources.

The various physicians must carry out exactly the treatment procedure which the directing physician has indicated, unless some unforeseen complication makes this impossible. The treatment given should be recorded as to date and dosage on the record to be retained by the patient, and returned ultimately to the original physician. No comments of any sort as to the suitability of the treatment or the competency of other physicians should be made to the patient, nor should the details of his case be discussed with him. If he insists on asking questions, he should be told to consult the original physician, either in person or by mail. If a change in the planned outline of treatment is essential for any reason, it should be made; but the original physician should be notified at once of the alteration and the reason for it. Each physician, no matter what his professional eminence or particular expertness, should regard himself as the temporary assistant of the physician primarily responsible for the management of the patient, and should conduct himself accordingly.

Syphilotherapy: Recent advances. H. N. Cole. *J. A. M. A.*, Chicago, 117: 1091-1095, Sept. 27, 1941.

Cole has based his discussion on the two recent publications of Stokes and Ingraham in which they have analyzed correspondence received from colleagues and lay persons (*Ven. Dis. Inform.*, 21: 129-156, 1940), and also on a review by Padget of a fairly large group of treated syphilitic patients who have been observed for a long period of time (*J. A. M. A.* 116: 7-11, Jan. 4, 1941.) He discusses the treatment of syphilis in pregnancy and of congenital syphilis, drugs used in the treatment of early syphilis,

and long-term management of early syphilis.

The conclusions reached by Cole are as follows: A safe, short cure for early syphilis is greatly needed. This would obviate lapses in treatment, infectious relapses, and uncured syphilis. Until such a cure has been found and carefully checked, it is advisable to rely on slower but time-tested and proved methods. Padget's survey has brought out several salient features: (1) If possible, the diagnosis in early syphilis should be made by the dark-field examination; it must be remembered that one test does not rule out syphilis. If indicated, daily examinations are in order. (2) The outcome in early syphilis depends not only on the number of arsenical injections but also on the "time space" in which they are given. (3) The treatment in uncomplicated cases should run somewhat as follows: Twelve injections of an arsenical, followed by 6 weekly injections of bismuth subsalicylate, 10 of an arsenical, 8 of the bismuth, 10 of an arsenical, 10 of the bismuth, 8 of an arsenical and 12 of the bismuth. (4) The first 3 injections of the arsenical should be given 3 days apart, thereafter, with neoarsphenamine or arsphenamine once a week, with mapharsen every 5 days. With the last arsenical in a course the first injection of a bismuth compound should be given. (5) There will be 90 percent plus cures if the diagnosis is made in the seronegative primary phase and if the treatment is of the continuous, overlapping type and consists of 40 injections of an arsenical and of a bismuth compound.

An evaluation of the massive dose therapy of early syphilis. David C. Elliott, George Baehr, Loren W. Shaffer, Glenn S. Usher and A. Allan Lough. *J. A. M. A.*, Chicago, 117: 1160-1164, Oct. 4, 1941.

The authors offer this paper as a progress report on the results and observations of massive mapharsen therapy in 968 cases of primary and secondary syphilis not complicated with pregnancy which have been treated in the 13 hospitals

which are cooperating in a study of this therapy. A total of 1,600 patients have been known to the authors, but they are considering the 968. A few of the patients had received one or two injections of an arsenical prior to hospital admission. The total amount of mapharsen administered in the treatment varied from 250 to 1,250 mg., with 1,200 mg. as the amount most frequently used. Three different injection schedules for administering the arsenical were employed: (1) Slow intravenous drip, consisting of continuous injection of 2,000 cc. of solution during 7 to 10 hours daily; (2) rapid intravenous drip, consisting of a continuous injection of approximately 1,000 cc. of solution during 1 to not more than 3 hours daily; and (3) multiple injection method, consisting of one or more rapid injections by syringe technic of small amounts of solution daily. Since there were not enough cases in each of these groups for comparisons, this report is based on the 968 cases as a group. Of the 968 cases, 13 percent were seronegative primary, 28 percent seropositive primary, and 59 percent in the secondary stage; 72 percent of the 968 patients were men.

During the hospital period patients were observed closely for reactions; urine and blood studies were performed frequently. With the exception of a few cases of peripheral neuritis, all reactions to treatment occurred during or within 2 to 3 days after completion of treatment. In the total of 1,600 patients that have received massive dose therapy 5 (0.3 percent) treatment deaths have been reported, and these cases presented a clinical picture of hemorrhagic encephalitis. Sometime during treatment from 90 to 95 percent of the patients experienced some reaction. The reactions were mild and seldom interfered with the treatment schedule. There was little evidence of liver damage and significant renal damage. Dermatitis exfoliativa, blood dyscrasias or nitritoid reactions were not observed.

Although the period of observation is still too brief to permit final evaluation,

the clinical and serologic failures occurring within 6 months to a year after a single course of massive dose therapy will probably be between 5 and 15 percent when 1,200 mg. of mapharsen is used, according to the authors' estimate.

The writers feel that the public health importance of a method which offers the possibility of eliminating the infection in at least 85 percent of the early cases of syphilis with 5 successive days of treatment and presents an opportunity for the rapid control of this disease, warrants the continuation of the present study in well-organized treatment centers.

In the discussion Rattner reports that 5 pregnant women have received the massive dose therapy at the Cook County Hospital with no untoward effects on the pregnancy. Baehr cautions that the technic should not be released to the general profession at present, not until wider hospital experience has been gained. Spiller reports one death from encephalitis among 70 cases which he has treated. He modifies the treatment by giving soluble bismuth 3 times a week for about 8 to 10 weeks following the massive dose therapy. Strauss and Sadusk report that practically all the new cases which have occurred in New Haven in the last 18 months have been sent to the hospital for this treatment and the courses have been satisfactory. There have been 13 cases of primary or secondary syphilis including one pregnant woman. Goldblatt reports the treatment of 100 Negro patients, to whom 1,200 mg. of mapharsen was administered by daily single injections of 100 mg. These patients were unselected and included some early cardiovascular cases and varied types of neurosyphilis. The results in the latent and late cases were disappointing. The results in external manifestations, such as gummas, were dramatic. A gumma of the face of 2 years' duration healed within 6 days. In Dallas, Schoch has been using the syringe method for the past 11 months, giving 120 mg. of mapharsen for 10 consecutive days. He reports 80 percent cures, 10 percent failures and 10 percent as yet undetermined of the

70 who have completed treatment. There was 1 case of hemorrhagic encephalitis, with prompt recovery. The syringe technique is a necessity in his part of the country because of the scarcity of hospital beds available for intravenous drip. Schamberg cautions against the indiscriminate use of this therapy in late syphilis. He says that in most forms of late syphilis the problem of infectiousness is negligible and speedy therapeutics is of little value and may be harmful. Hyman believes that the toxicity of the five-day treatment is decidedly less than that of routine conservative treatment with the possible exception of cerebral manifestations, and he is convinced that this complication would be found to occur equally in all forms of routine arsenotherapy.

Massive dose arsenotherapy of early syphilis by intravenous drip method. Recapitulation of the data (1933 to 1941). William Leifer, Louis Chargin and Harold Thomas Hyman. *J. A. M. A.*, Chicago, 117: 1154-1160, Oct. 4, 1941.

Four groups of patients treated by the intravenous method are included in the summary: Group 1, studied in 1933, 25 patients given an average of 4 gm. of neoarsphenamine over the course of 5 days; group 2, in 1938, 86 men treated in the same manner; group 3, in 1938 and 1939, 157 patients who received an approximate average of 700 mg. of mapharsen; group 4, in 1939 and 1940, 118 patients who received 1,200 mg. mapharsen. (This group included 4 patients who had been reported also in the neoarsphenamine series.) A total of 382 individuals were treated. With one exception all patients were men, and the majority were between 20 and 35 years old. There was 1 death from treatment.

Twelve percent of the men, on admission, were in the seronegative primary stage, most favorable from a therapeutic standpoint. The 25 patients in group 1 were not classified as to the stage of the disease except one who was in the sero-

negative primary stage; the other 24 had seropositive primary or secondary syphilis. In the other groups, 142 were in the seropositive primary stage and 174 in the secondary phase.

The minor and annoying toxicologic phenomena included local reactions, primary and secondary fever, toxicodermas, nausea and vomiting. There was significantly less disturbance in the mapharsen series. Of the moderately severe toxic symptoms, peripheral neuritis (which occurred in more than one-third of the patients who received neoarsphenamine) was reduced to a negligible incidence of mild paresthesia in the mapharsen series. Of the grave untoward reactions associated with arsenotherapy only the cerebral symptoms were encountered. Such complications appeared in 5 patients, representing 1.8 percent of the neoarsphenamine and 1.1 percent of the mapharsen series. In 1 patient, a Negro who received neoarsphenamine, the results were fatal.

For the therapeutic results the statistics from the series are presented in the most unfavorable light. Eight possible reinfections are regarded as infectious relapses, and patients who were clinically well but whose serologic reactions remained positive were classified as unsatisfactory. Under such considerations and taking the series as a unit, 81 percent of the patients had a completely satisfactory course. Including favorable results from re-treatment in an additional 15 cases, the total number of satisfactory results approximates 88 percent for the entire series. Satisfactory results from a single course were recorded for 89 percent of the patients given neoarsphenamine, 79 percent of the small-dose mapharsen group, and 83 percent of the large-dose mapharsen group. There were 17 patients whose treatment was an irrevocable failure after primary and secondary courses of treatment, and more than half of these may well have had a reinfection. Five of this group received less than 600 mg. of mapharsen, 1 received 700, and 2 approximately 800 mg. The original failure might not have existed had these patients received

the original dose of 1,200 mg., and a definite policy for re-treatment might have lowered the percentage. One of the group of failures had a positive reaction of the spinal fluid, but with this exception the spinal fluid of every patient became perfectly clear. The treatment of none of the 41 patients with seronegative primary syphilis, 2 of whom were re-treated with massive dose arsenotherapy, was a failure.

With the exception of the infectious relapse at the site of original inoculation, no organic manifestation of syphilis has yet been noted. The patients in group 1 were examined at the end of 5 years, and many of those in group 2 have passed 3 years of observation.

A recommendation for the use of a consolidated graphic progress chart toward the more efficient management of gonorrhea in the male. James P. Pappas, Mil. Surgeon, Washington, 89: 664-668, Oct. 1941.

No civilian clinic can approach the control the Army has over its gonorrheal patients both during the treatment period and for months, if not years, afterward. This provides an opportunity to contribute toward a more thorough evaluation of the effectiveness of treatment by the sulfonamide drugs which should be utilized. Ordinary progress notes are relatively unsatisfactory and time-consuming. Failure to have a complete clinical picture which can be easily read is as responsible for unsatisfactory results in the therapy of gonorrhea as any other single factor.

Pappas presents an excellent graphic chart, based on experience of the past 3 years, which gives at a glance a full, complete and exact picture of the status and of all pertinent aspects of any gonorrheal infection. On it the dosage of the drug is noted in grams daily. Irrigations or instillations are easily noted by checkmarks; the strength, and whether administered into the anterior or anteroposterior urethra, can be indicated by a few descriptive figures. The result of

prostatic smear is indicated by a fraction, the numerator indicating the presence or absence of the gonococcus and the denominator the degree of inflammation or suppuration. The amount of discharge is noted by the relative grading from "1" to "4", with "D" signifying that a drop can be expressed from the urethra throughout the day, while "D-" conveys the information that the patient is "dry" except for the "morning drop."

Modification of this form could easily be made to suit individual preferences, and the form can be easily typed or mimeographed on the present Form 551 MD. For the purpose of follow-up of cases or for collecting data for study a duplicate of the chart can be prepared. On the reverse side of this duplicate chart, a summary of the case and the follow-up notes could be entered. When a soldier is transferred, the duplicate form (gonorrhea register) could be forwarded to his new station, as is now the practice with syphilis registers (Form 78 MD).

Toxic depression of the myeloid elements following therapy with the sulfonamides; report of 8 cases. Solomon S. Rinkoff and Maxwell Spring. Ann. Int. Med., Lancaster, 15: 89-107, July 1941.

The authors present the cases of six patients illustrating the toxic effect of the sulfonamides on the myeloid elements. Three of these patients had taken sulfanilamide, two had taken sulfapyridine, and one had taken a combination of sulfapyridine and neoprontosil.

Two cases of agranulocytosis followed the use of 4 and 45 gm. of sulfanilamide given over a period of 1 and 21 days, respectively. The patients did not respond to treatment and apparently died of the blood dyscrasia. One case of leukopenia developed after 65 grains (4.3 gm.) of sulfanilamide had been given over a period of 24 hours.

One patient had leukopenia after the ingestion of 6 gm. of sulfapyridine over a period of 17 hours. In another patient, 89 gm. of the drug taken over a period

of 17 days resulted in agranulocytosis. This condition did not respond to therapy and apparently hastened the patient's death. Twenty gm. of sulfapyridine plus 6 gm. of neoprontosil taken over a period of 14 days caused a leukopenia in another patient.

Two additional cases are also reported in which there was probably agranulocytosis following sulfanilamide and neoprontosil treatment. Both patients were given about 3.5 gm. of the two drugs. One of the patients died, and the other recovered.

During the period, January 1939 to February 1941, 768 patients were given sulfonamide drugs in The Bronx Hospital. Five patients (0.65 percent) had toxic reactions on the myeloid elements. Patients who had received such treatment before admission to the hospital are not included in this group.

The authors make the following conclusions:

1. Sulfonamide drugs have a definite toxic effect on the bone marrow, hence they should be used only when there is a definite indication. Promiscuous use for minor ailments such as respiratory infections, tonsillitis, grippe, is condemned.

2. Frequent blood examinations should be made not only while the drug is being given, but for 5 to 10 days after it has been discontinued.

3. The dosage of the drug, not the blood concentration, is probably the factor that determines whether a toxic manifestation will occur in a susceptible person.

4. Although a small dose may cause leukopenia or a fatal granulocytopenia (a total dosage of 4 gm. in two of these cases), these toxic effects on the bone marrow usually occur after prolonged use of the drugs, especially in cases in which the disease itself has a deleterious effect upon the hemopoietic system.

5. In view of the incidence of the more severe toxic manifestations of the sulfonamides, the authors believe that the physician is seldom justified in using these drugs prophylactically.

PATHOLOGY

Rupture of aorta into the pulmonary artery with long survival. Paul D. White, Francis L. Chamberlain and Saul R. Kelson. *Ann. Int. Med.*, Lancaster, 15: 589-597, Sept. 1941.

The case is reported here of a 74-year old Negro man who died in 1938 of heart failure, 21 months after onset of cardiac symptoms and 8 months after the correct clinical diagnosis was made of rupture of a syphilitic aneurysm of the ascending aorta into the pulmonary artery. This case is of note because of the unusual longevity both in age of patient and in survival after the rupture, and because only two cases previously had been correctly diagnosed ante mortem.

The patient had entered Massachusetts General Hospital in 1933, in his 70th year because of ulcers of the right leg following varicose veins and an infected scratch of a year before. He had had no dyspnea, chest pain, or palpitation, but examination revealed moderate enlargement of the heart, aortic systolic and diastolic murmurs, a blood pressure of 195 mm. mercury systolic and 55 mm. diastolic, a positive Hinton reaction, and by roentgen ray slight aneurysmal dilatation of the ascending aorta. In 3 weeks he was discharged with the ulcers almost wholly healed after treatment by rest, potassium iodide and mercury by mouth, and soothing ointments to the leg. He continued the potassium iodide and mercury for a few months.

In January 1937, he was taken ill with what he thought was a cold, accompanied by palpitation and dyspnea to the point of orthopnea. In April he became much worse, with substernal pain and restlessness quickly followed by edema of the legs. In May 1937 he reentered the hospital very ill. His heart was found to be much larger than before and the roentgenogram showed marked prominence of the pulmonary artery and lung

hilus shadows not present in the earlier picture. He improved rapidly with rest, digitalization, and salyrgan diuresis, and was discharged in a few days. He remained improved for 6 months.

In January 1938, he rapidly grew worse again and reentered the hospital in February in severe congestive failure. In addition to the auscultatory findings previously found, an "aortic" systolic thrill was noted. The blood pressure varied from 130 to 180 mm. mercury systolic and about 60 diastolic. In February, it was noted that the murmur and thrill in the pulmonary area were really continuous and not just systolic and diastolic. A tentative diagnosis was made of rupture of an aortic aneurysm into the pulmonary artery. The patient remained crippled with heart failure, and died on October 7, 1938.

At autopsy, the heart weighed 885 gm. and was greatly enlarged in all diameters, with particular prominence in the region of the pulmonary conus. Its cavities had approximately three times normal volume, and all valve rings were dilated. The left ventricular wall measured up to 19 mm. in thickness, the right up to 7 mm. The aortic valve was slightly thickened along its free edge. The aortic sinuses were greatly dilated, with a few small nodular calcific deposits at the base of the right and posterior cusps. The orifice of the right coronary artery was completely occluded by syphilitic and atherosclerotic scarring, and the vessel itself was small and collapsed. The pulmonary artery was markedly dilated, measuring 8.5 cm. in circumference at a level 3 cm. above the pulmonary valve ring. Five mm. above the insertion of the valve cusps and slightly posterior and to the right of the right anterior valve commissure was a roughly oval opening 5 mm. by 6 mm. with smooth, slightly raised margins.

There was marked diffuse aneurysmal dilatation of the ascending aorta and arch, and to a lesser extent, of the descending portion. The aorta and arch showed changes typical of syphilitic aortitis. There were numerous linear, puckering, spoke-like crenations, and smooth

pearly elevated patches, with many soft yellow atheromatous deposits, ulcerated in places. Above the right posterior commissure was a secondary saccular aneurysmal pocket 2.3 cm. across by 2.8 cm. high by 2.1 cm. deep, with thickened smooth edges. A probe within the right coronary artery passed behind and above this sac to an occluded orifice immediately to the right. Above the commissure between the right and left anterior cusps was a less sharply defined secondary aneurysmal pouch, measuring 3.5 cm. across by 4.0 cm. long by 2.0 cm. deep, with a small out-pocketing from its upper right margin. In its anterior lower margin, 1.5 cm. above the aortic valve ring, was a smooth-edged oval opening, surrounded by puckered yellowish plaques. This opened into the pulmonary artery and was the same opening previously described there. Above and slightly to the left of the posterior aortic cusp, with its lower margin 1.7 cm. above the free edge of the cusp, was a smooth-lipped opening into the aortic wall, 9 by 7 mm. This ended in a blind pocket in the septum between the aorta and the right auricle, with a depth of 3 mm., partly filled with projecting irregular clot. The descending aorta measured 7.5 cm. in circumference, and showed numerous atherosclerotic plaques but very few puckerings suggesting syphilis. Atheromatous changes were most plentiful in the abdominal aorta, particularly at its bifurcation, where ulceration was extensive.

Microscopically, the myocardium showed one small area of fibrosis. The aortic wall showed perivascular lymphocytic infiltration characteristic of syphilis. There was fragmentation of the elastic fibers with medial degeneration and hyalinization. There were areas of intimal thickening and hyalinization, and extensive areas of cholesterol deposit deep in the media, with necrosis of the surrounding tissue and a few small foci of calcification in the media.

In the last 25 years there have been a dozen case reports of this rare condition, the last one in 1938. Before 1913,

there had been about 50 cases on record. Only two previously, so far as the authors knew, had been definitely diagnosed ante mortem. These were reported in 1861 and in 1924, respectively. However, the chief diagnostic clue (the development of a continuous murmur in the pulmonary valve area) was clearly pointed out by James Hope in 1839 in the third edition of his work on diseases of the heart and great vessels.

LABORATORY RESEARCH

Cerebrospinal fluid protein values determined by tyrosine equivalent method. T. U. Marron. *Am. J. M. Sc., Philadelphia*, 202: 330-333, Sept. 1941.

The author reports the results of total protein determinations by the tyrosine equivalent method (Johnson and Gibson's modification) of 550 cerebrospinal fluids taken from healthy persons and from sick patients. The upper limit of normal values was found to be 46.0 mg. per 100 cc. The ranges for pathologic values agreed well with generally accepted figures in the literature. The average protein values for females was less than that for males. Dehydration did not appreciably affect the protein concentration.

Forty of the persons tested had neurosyphilis (all types). The average protein concentration in mg. per 100 cc. was 56.8, and the range was 11.0 to 156.0. Twenty-one of these persons had concentrations of above 46.0 mg. per 100 cc.

Flocculation tests for syphilis (plant sap reactions). Edward L. Breazeale, Theodore R. Reusser and James F. Breazeale. *Southwestern Med., El Paso*, 25: 253, 256-257, Aug. 1941.

Probably the greatest advancement in the serology of syphilis in the past few years has been the recognition of the ex-

istence of biologically false positive tests in nonsyphilitic individuals. Neither the exact cause of these false positive tests in diseases other than syphilis nor the occurrence of positive reactions with most animal serums has been satisfactorily explained:

The authors report a study they have conducted for the purpose of showing that (a) the test employed in the diagnosis of syphilis is purely an empirical procedure and that substances other than the so-called reagin of syphilis can produce positive flocculation tests; (b) these substances which are responsible for the production of positive flocculation tests are found widely distributed in nature, and (c) these reagin-like substances are found in high concentration in plant saps.

Saps were extracted from stems and leaves of various plants by use of a Carver hydraulic plant press. Kline diagnostic, Mazzini, Leiboff, and the rapid Hinton and Wassermann tests were run on three separate samples of each species examined. None of the saps were inactivated. The various saps were then diluted, using normal saline, until they no longer gave a positive test. Of the 50 plant saps studied, 46 gave positive serologic results with the Kline, Mazzini, Leiboff, and Hinton tests. None of the saps gave positive Wassermann reactions. The reagin-like substance in the plant saps was present in varying amounts as shown by the titers obtained.

There is no exact explanation of the observed phenomenon at this time. However, experiments on plant finding, the reaction of the sap from the various parts of the plant, the age of the plant, and the effect of supersonic waves on plant saps as regards the flocculation tests are now in progress.

The viability of the spirochetes of syphilis and yaws in desiccated blood serum. Thomas B. Turner, Johannes H. Bauer and Fred C. Kluth. *Am. J. M. Sc., Philadelphia*, 202: 416-423, Sept. 1941.

In both civil and military medical practice, transfusions are being made to an

increasing extent with refrigerated whole blood and with blood serum or plasma which has been stored in the liquid or desiccated state. Since, under conditions of emergency, it may not always be possible to select blood donors carefully with respect to their freedom from syphilis, experiments were designed to determine the probable limits of safety (with regard to the transmissibility of syphilis) in the use of desiccated blood serum for transfusion.

In experiments made several years ago by Turner and coworkers, testicular emulsions rich in *T. pallidum* were frozen and desiccated. Upon rehydration, most of the spirochetes were distorted and 9 of 10 specimens tested failed to produce lesions when inoculated into normal rabbits. One specimen tested 24 hours after drying was started produced lesions after a long incubation period. This result was attributed to incomplete dehydration of the specimen.

In recent experiments, reported in this paper, the infectivity of virulent *T. pallidum* suspended in rabbit serum was tested before and 3 to 5 days after desiccation. Material from each of 9 specimens produced lesions in rabbits before desiccation. Three to 5 days after freezing and drying in an efficient desiccating apparatus, rabbits were inoculated with from 6 to 65 times the amount used for the control animals. None of 18 rabbits inoculated with desiccated material developed a syphilitic lesion, and their lymph nodes were not infectious for normal rabbits.

Of six rabbits similarly inoculated with desiccated *T. pertenuis* from three different sources, none developed lesions, and their lymph nodes were not infectious for normal rabbits.

The authors conclude that *T. pallidum* and probably *T. pertenuis* are commonly killed by the process of freezing and desiccation, even when the method is such that the viability of many other bacteria and viruses is retained. Transfusion of desiccated blood serum or plasma is, therefore, probably without risk as regards the

transmission of syphilis or yaws, even though the material be obtained from an infected donor.

Sobisminol solution and water-soluble potassium bismuth tartrate by oral and intramuscular administration in the treatment of experimental rabbit syphilis. John A. Kolmer, Herman Brown and Anna M. Rule. Am. J. Syph., Gonorr. & Ven. Dis., St. Louis, 25: 595-606, Sept. 1941.

The authors found that the maximum single tolerated dose of sobisminol for rats by intramuscular injection was 0.5 gm. of compound (corresponding to 0.105 gm. of elemental bismuth) per kg. of weight. The maximum single tolerated dose of water-soluble potassium bismuth tartrate was about 0.4 gm. per kg. (equivalent to 0.256 gm. elemental bismuth). In terms of elemental bismuth, therefore, potassium bismuth tartrate was about one-half as toxic as sobisminol (sodium bismuthate soluble) by this route of administration.

According to the authors, the oral administration of sobisminol solution and water-soluble potassium bismuth tartrate in repeated doses to rabbits with acute syphilitic orchitis is capable of effecting biologic cure. The minimal curative dose of sobisminol for such rabbits by oral administration was about 2 gm. per kg. of weight (equivalent to about 0.4 gm. elemental bismuth) divided into 20 doses given at daily intervals. The minimal curative dose of water-soluble potassium bismuth tartrate for such rabbits by oral administration was between 0.48 and 0.72 gm. per kg. of weight (equivalent to 0.3 to 0.46 gm. elemental bismuth) divided into 24 doses given at daily intervals. In terms of elemental bismuth, both compounds, therefore, are about equal in therapeutic activity by oral administration.

The minimal single curative dose of sobisminol by intramuscular injection to rabbits with acute syphilitic orchitis was about 0.2 gm. per kg. of weight (equivalent to 0.004 gm. of elemental bismuth).

The minimal single curative dose of water-soluble potassium bismuth tartrate by intramuscular injection to such rabbits was about 0.006 gm. per kg. of weight (equivalent to about 0.00384 gm. elemental bismuth). In terms of elemental bismuth both compounds, therefore, were about equal in therapeutic activity by this route of administration.

Both sobisminol and water-soluble potassium bismuth tartrate were absorbed from the gastrointestinal tract of the syphilitic rabbits as shown by the excretion of bismuth in the urine.

The biologic cure of rabbits with acute syphilitic orchitis required the oral administration of sufficient sobisminol to maintain a daily total urinary excretion of at least 0.064 to 0.66 mg. elemental bismuth for 1 to 19 days. Sufficient potassium bismuth tartrate was required to give a daily total urinary excretion of at least 0.04 to 0.63 mg. elemental bismuth for 1 to 35 days. Both compounds were found to have about equal values in relation to the urinary excretion of bismuth by this route of administration.

The biologic cure of rabbits with acute syphilitic orchitis required the single intramuscular injection of sufficient sobisminol to maintain a daily total urinary excretion of 0.096 to 0.972 mg. elemental bismuth over a period of 1 to 35 days. In the case of water-soluble bismuth tartrate, it was found that the single dose must be sufficient to maintain a daily total urinary excretion of 0.042 to 0.6 mg. for at least 1 to 28 days.

Both compounds by oral administration were found to possess about equal degrees of therapeutic effectiveness in the treatment of acute syphilitic orchitis of rabbits. The authors state that apparently either compound may be used in the treatment of human syphilis. One capsule (0.75 gm.) of sobisminol mass in terms of elemental bismuth is the equivalent of about 0.25 gm. of water-soluble potassium bismuth tartrate.

PUBLIC HEALTH ADMINISTRATION

Annual report of the Surgeon General, U. S. Navy. Statistics of diseases and injuries for the calendar year 1939. Washington, 1941.

Venereal diseases (pp. 67-98).—Venereal diseases occupied second place among all causes of morbidity and contributed the second largest number of sick days of any group. These diseases were responsible for 21.03 percent of admissions for all causes and 13.02 percent of total sick days. The admission rate for 1939 was 85.87 per 1,000. There were 1,957 new admissions for chancroidal infections; 8,569, for gonococcus infections; 1,930, for syphilis; 66, for syphilis (seropositive only); 315, for venereal lymphogranuloma; 8, for venereal verruca acuminata; and 2, for venereal balanoposthitis, a total of 12,847 cases admitted during the year. These admissions do not include infections acquired prior to enlistment. There was 1 case of chancroidal infection, 46 cases of gonococcus infection, 17 cases of syphilis, and 16 cases of syphilis (seropositive only) reported as existing prior to enlistment, and these figures increased the total venereal rate 0.53 per 1,000.

There were 156,506 sick days reported for these diseases. The daily average of persons on the sick list was 2.87 per 1,000. This is 31.34 percent less than the median rate for the preceding 9 years (4.18). The noneffective ratio per 100,000 caused by chancroidal infections was 26.92; for gonococcus infections, 193.52; for syphilis, 52.70; for syphilis (seropositive only), 1.77. There were 14,703 sick days recorded for chancroidal infections resulting in 6.2 sick days per case; 105,692 sick days for gonococcus infections, or 9.5 days per case; 28,783 sick days for syphilis, or 12.6 days per case; 966 sick days recorded for syphilis (seropositive only), or 10.9 days

per case; for venereal verruca acuminata, 205 sick days, or 22.8 days per case; for venereal lymphogranuloma, 6,045 days, or 16.4 days per case; for venereal balanoposthitis, 90 days or 18 sick days per case.

The rate for all venereal diseases per 1,000 admissions was 100.40 for the Navy and 69.76 for the Marine Corps. For the enlisted personnel the admission rate, as compared with the median rate 1930-38, showed for the Navy an increase of 31.64 percent in chancroidal infections, 3.04 percent for gonococcus infections, and a decrease of 35.76 percent for syphilis; for the Marine Corps a decrease in percentages of 28.16, of 15.09, and of 55.03 respectively.

According to reports submitted on Dec. 31, 1939 by all ships and shore stations there were 15,322 naval personnel with a history of syphilis. A total of 7,616 persons were treated for syphilis with arsenicals, and 6,466 with heavy metal compounds. During the year 50 reactions were reported following the use of arsenical compounds, classified as follows: Neoarsphenamine, 4 fatal, 11 severe, and 21 mild; mapharsen, 5 severe, and 9 mild.

There were 6 cases of dementia paralytica remaining from last year, with 1,827 sick days. There were 30 cases of neurosyphilis (serologic) and 42 of cerebrospinal syphilis (undifferentiated).

Annual report of the Surgeon General, U. S. Navy. Statistics of diseases and injuries for the calendar year 1939. Washington, 1941.

Comments of medical officers taken from annual sanitary reports (pp. 75-93).— According to these comments, it is felt that the passage of premarital examination laws by the different States will be an incentive for the men of the Navy to avail themselves of the prophylactic measures provided against venereal disease infection. The commanding officers of many of the ships have been particularly interested in the prevention of venereal diseases. They have given many talks to the men relative to the cause, symptoms, and after-effects of venereal infection and special instruction regarding

methods of prevention. The ship's welfare fund supplies condoms and prophylactic tubes on many ships. It seems to be the general opinion that every case of infection can be traced to either delayed or faulty application of prophylactic measures or both, and the medical officers are constantly urged to instruct and educate their crews in the necessity for prompt and proper application of these measures. U. S. S. Lexington reported that not a single case of venereal disease developed among 273 men who reported exposure and took prophylaxis aboard ship; while 24 who had not taken the recommended chemical prophylaxis were infected. Similar reports were given from other ships. The old method of chemical prophylaxis is gradually being supplemented by mechanical prophylaxis. There is occasional objection to the carrying of sanitubes because of the limited pocket space and because they occasionally break, spotting the uniform. There is no question of the value of prophylaxis including protargol taken on return to the ship, if the time between exposure and the time of prophylaxis is not too great. It is believed that a packet containing a condom with a sanitube half the size of the present tube would give the maximum protection.

The rate for venereal diseases in the Atlantic Squadron and Scouting Force is high when compared with the Battle Force and the Base Force, probably due to the highly infectious nature of the ports visited by the two Forces. After the arrival of the U. S. S. Trenton in Lisbon in Sept. 1939 there was such an increase in the rate of admissions for venereal disease that an order was issued placing all new admissions for venereal diseases on the sick list for at least 2 weeks on misconduct with retention on the venereal restricted list for at least 3 months in order to protect the remainder of the crew. Sanitubes were distributed at the gangway and condoms were made available at the ship's service store and sick bay.

The U. S. S. West Virginia reported a decrease in the admission rate during the cruise to the Caribbean, probably due to

a combination of mechanical prophylaxis, limited liberty, and lack of inclination for or fear of exposure with the native prostitutes. Due to the very fine spirit of cooperation of the local health authorities in the Puget Sound area the increase did not reach the expected rate by at least 40 percent. The careful supervision by the police of Honolulu over authorized houses of prostitution produced a marked decrease in rate. The higher rate for the Atlantic Squadron is attributed to the location of a ship rather than to the vagaries of the personnel. Men feel a certain security in home ports as compared to foreign ports and are inclined to be more negligent.

In the Base Force all cases of gonococcus infections and open venereal lesions occurring on ships not carrying a medical officer are transferred to a ship with a medical officer or to a hospital.

Various preparations of sulfanilamide have been used in the treatment of Neisserian infections. Many relapses occurred among apparently cured cases. Six out of 8 sulfanilamide reactions on the Lexington occurred in patients whose blood was type "A".

The U. S. S. Hannibal on Special Duty reported several cases of inguinal lymphadenitis contracted in Curaçao. These cases were clinically venereal lymphogranuloma, though they failed to react to Frei antigen, and caused a great economic loss to the ship. The disease is very prevalent among Negro prostitutes in the West Indies.

Control of the venereal diseases in civilian areas adjacent to concentrations of armed forces. A. B. Price and F. J. Weber. *Am. J. Pub. Health*, New York, 31: 912-916, Sept. 1941.

For a year the authors were actively engaged in venereal disease control in two of the large maneuver areas in the southern States. As a result of this work they recognize the necessity of certain procedures and have been in a position to judge the efficacy of such measures in the control of venereal diseases. They discuss

here the special nature of venereal disease control in training areas, together with what they believe to be practical proposals for its solution.

Available records indicate that the great majority of sexual exposures of enlisted men is with prostitutes. In one of the areas studied during the winter of 1939-1940, 112 of 120 men questioned named a prostitute as the source of their infection. In this same area, of 180 prostitutes examined, 37 percent were found to be infected with syphilis and 10 percent with gonorrhea. Better diagnostic facilities would probably have revealed a greater number of gonococcal infections if vaginal smears only were examined in this group. In this area, of 120 soldiers infected with venereal disease who were questioned, 63 attributed their infection to prostitutes employed in "honky-tonks," while only 15 (12 percent) named inmates of recognized houses of prostitution.

In the maneuver areas studied, gonorrhea was found to be 4 to 10 times more prevalent than syphilis, while cases of chancroid, venereal lymphogranuloma and venereal granuloma were infrequent. The high attack rate for gonorrhea is a serious problem, since it means a loss of many days from duty and greatly increases the cost for hospitalization of troops.

The authors believe that the establishment of full-time local health services is essential to the development of a complete liaison between military and civilian authorities in matters of mutual health concern. In this way, venereal disease control can be correlated more effectively with other important health activities required to safeguard the health of both troops and civilians.

Military and naval officials should cooperate closely with local and State health authorities. Provision should be made for the exchange of pertinent information in health matters of mutual interest. In large training areas, this work can be done most effectively by a specially designated officer who assumes the responsibility for correlating public health

activities and who can effect the liaison between civilian and military or naval authorities.

Prostitution should be repressed in these areas by strict enforcement of existing laws backed up by responsible public opinion. Effective case-finding and contact-tracing procedures should be carried out which will bring infected civilians to treatment. A roster of all female employees in establishments serving food and drink should be prepared and routine examination made for communicable disease, including serologic tests for syphilis. Many sexual contacts of enlisted men are with such women.

In some places, certain physicians issue medical certificates to prostitutes asserting that they do not have venereal disease. Prostitutes with such certificates may regard them as a license to operate and use them to convince patrons that they are not diseased. By discussing this practice at a meeting of the local medical society, the health officer will usually succeed in having the practice discontinued.

Education of the public concerning venereal diseases, their treatment, and location of treatment centers is very important.

Due consideration should be given to the wider prevalence of gonorrhea. This disease has been much neglected in the past, and attempts at its control have been spasmodic.

Communities should cooperate by providing wholesome recreational facilities for men on leave.

Factors affecting industrial health. C. H. Watson. *Indust. Med.*, Chicago, 10: 403-410, Sept. 1941.

Watson discusses at length the fundamentals of an industrial health program. He says preplacement physical examinations play as large a part in influencing industrial health as any of the activities comprising medical supervision in industry. The serologic examination of the blood is well justified. Persons with syphilis should be identified in order that

they may be properly placed and routine check-up and care instituted. The individual with healed lesions, even if the serologic examination is positive, is a perfectly safe person for employment, provided the necessary follow-up with respect to treatment and successive blood examinations is carried out. It is recommended that in every instance in which the report of the blood test is positive, regardless of the type of test and in the absence of symptoms of syphilis, a second specimen should be sent to the laboratory for verification to establish whether the reaction is a normal biologic one or is truly specific.

A liberal policy of management with respect to the employment of syphilitic individuals should be established at the time of installing industry's public health responsibility.

Pharmacists of material aid in venereal disease control. *Eighty-ninth Annual Meeting of the American Pharmaceutical Association.* J. Am. Pharm. A., Washington, 2: 333-334, Aug. 1941.

Pharmacists, through their local, county, and State pharmaceutical associations, have responded enthusiastically to the request from the Joint Committee of the American Pharmaceutical Association and American Social Hygiene Association for cooperation in the national program for venereal disease control. Many health officers have expressed amazement at the amount and degree of cooperation that is available to them through retail pharmacies, once they begin to contact the local associations. Because both health departments and pharmacists are interested, the distribution of literature and of displays for windows goes on at a tremendous rate throughout the country.

Dr. Robert P. Fischelis, chairman of the committee, outlined the committee's work and called attention to the leaflets which have been distributed to men in the Army and the defense industries. These leaf-

lets caution the men on the dangers of venereal disease and advise them to obtain any necessary supplies from a pharmacy rather than from an unreliable source. The committee has prepared a leaflet entitled "A Tip from Your Pharmacist" to aid pharmacists in supplying proper information to those who seek

medication for self-treatment of venereal disease.

The appreciation of the U. S. Public Health Service to the pharmacists of the country for their part in the national program for venereal disease control was expressed in a letter which was read at the meeting.

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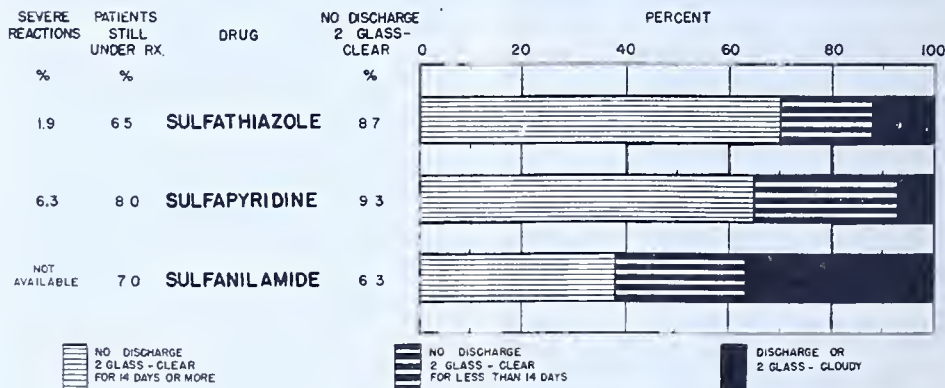
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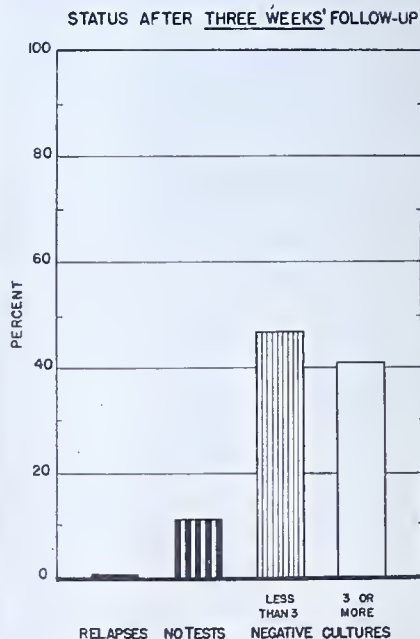
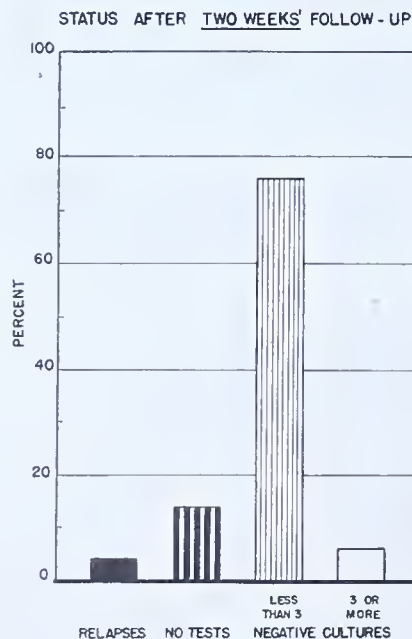
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